Simplified approach

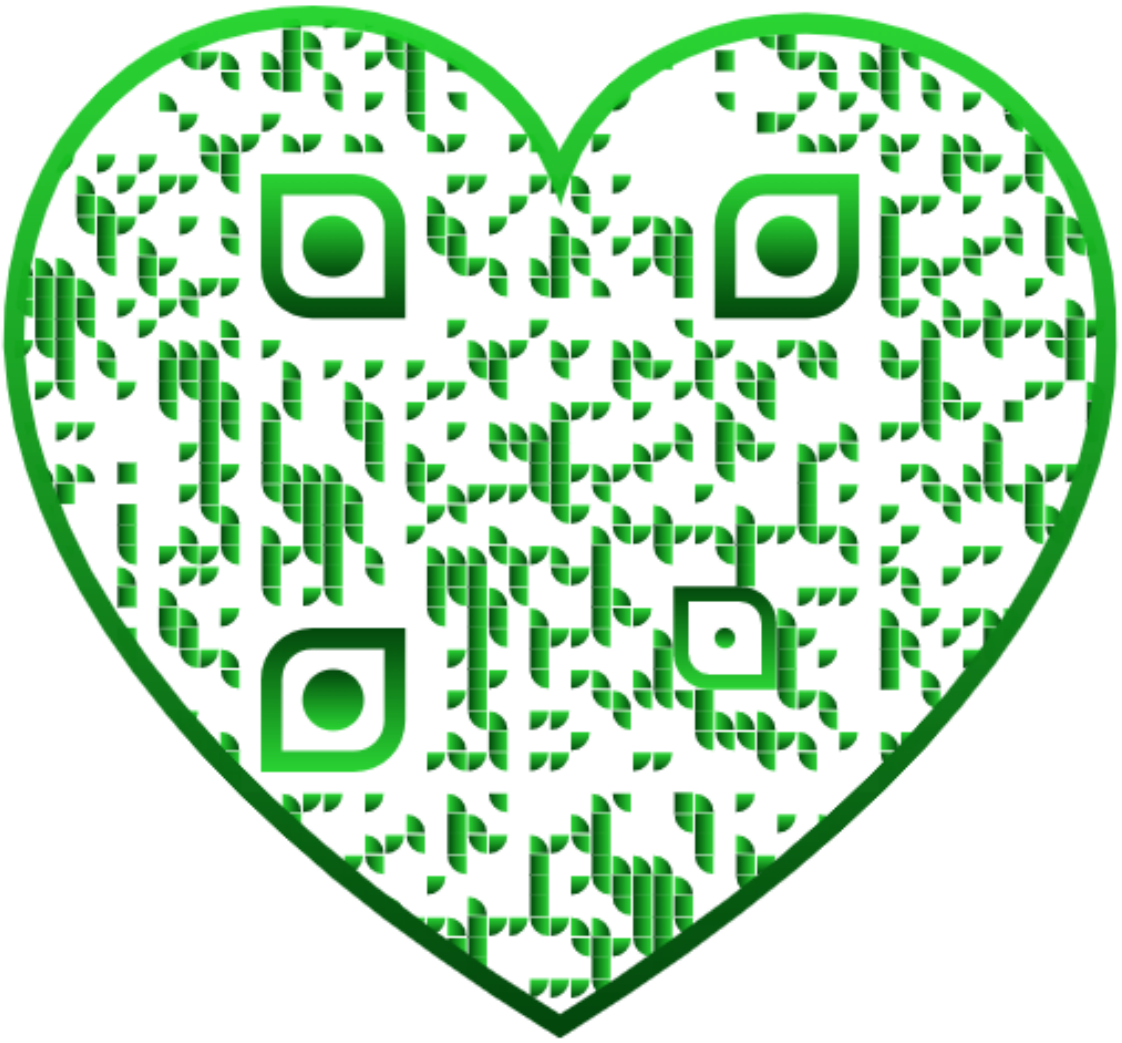
Mansoura Clinical Pharmacology

For Medical students

Edited by

Staff members of
Clinical Pharmacology Department
Faculty of Medicine
Mansoura University

Volume 1



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Preface

Clinical training for undergraduate students often focuses on diagnostic rather than therapeutic skills. Sometimes students are only expected to copy the prescribing behavior of their clinical teachers, or existing standard treatment guidelines, without explanation as to why certain treatment is chosen. Books may not be much help either. Pharmacology reference works and formularies are drug-centered, and although clinical textbooks and treatment guidelines are disease-centered and provide treatment recommendations, they rarely discuss why these therapies are chosen. Different sources may give contradictory advice.

This book in primarily intended for under graduate medical students who are about to enter the clinical phase of their studies. It will provide step by step guidance to the process of rational prescribing together with many illustrative examples. It teaches also skills that are necessary throughout a clinical career. Postgraduate students and practicing doctors may also find it a source of straightforward information.

I wish to acknowledge the ongoing efforts of my contributing authors, and we are deeply grateful to all those who have with such good grace given us their time and energy to supply valuable facts and opinions, they principally include:

- **Prof. Hussein El-Beltagi** who took over the preparation of all books since the 1st edition in 1995 including the revision process, printing control, distribution and selling control.
- **Assist. Prof. Mohamed-Hesham Daba** who took over the revision process and amendments of the last two editions.
- **Assist. Prof. Abdel-Motaal Fouda** who prepared the last two editions in a readable up-to-date text to provide essential information necessary throughout the clinical career.
- **Dr. Sameh Abdel-Ghany** who assisted in the revision process.

Much of any merit this book may have is due to the generosity of those named above.

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Mission and Vision

Our mission

The Clinical Pharmacology Department is seeking excellence and leadership in four major core activities: education, research, community service, and faculty and staff development. We are connecting basic medical sciences with clinical care through innovative and disciplined teaching of clinical pharmacology in an integrative manner

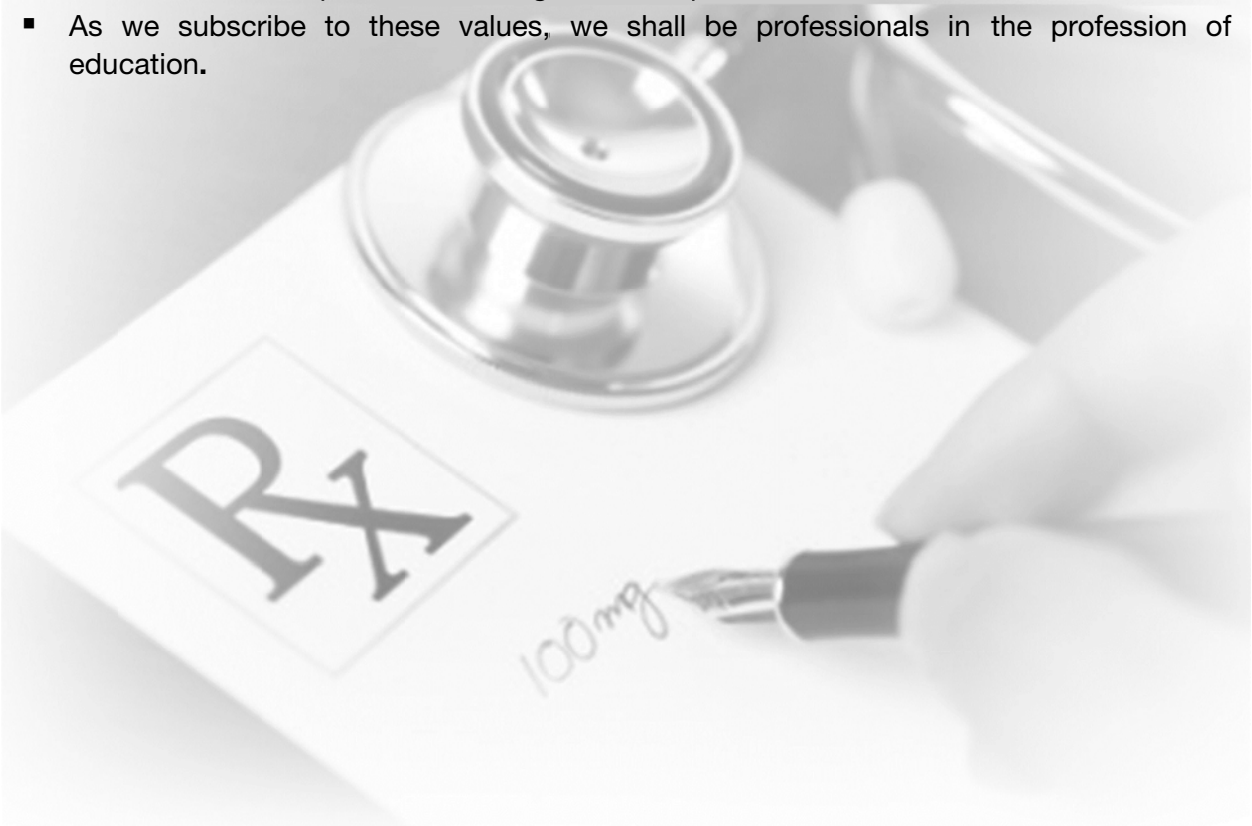
Our vision

The department of Clinical Pharmacology is aiming to be a premier academic model in the field of pharmacology and therapeutics in Egypt and Middle East through promoting use of the best therapeutics and developing newer experimental and clinical research projects.

Values

The guiding principles and beliefs for the department

- Excellence, creativity, innovation, fairness, honesty, transparency, collaboration, teamwork and lifelong learning
- Recognition that our student comes first
- All members of our department must see themselves as integral to the success of our mission and our department as integral to their personal success.
- As we subscribe to these values, we shall be professionals in the profession of education.



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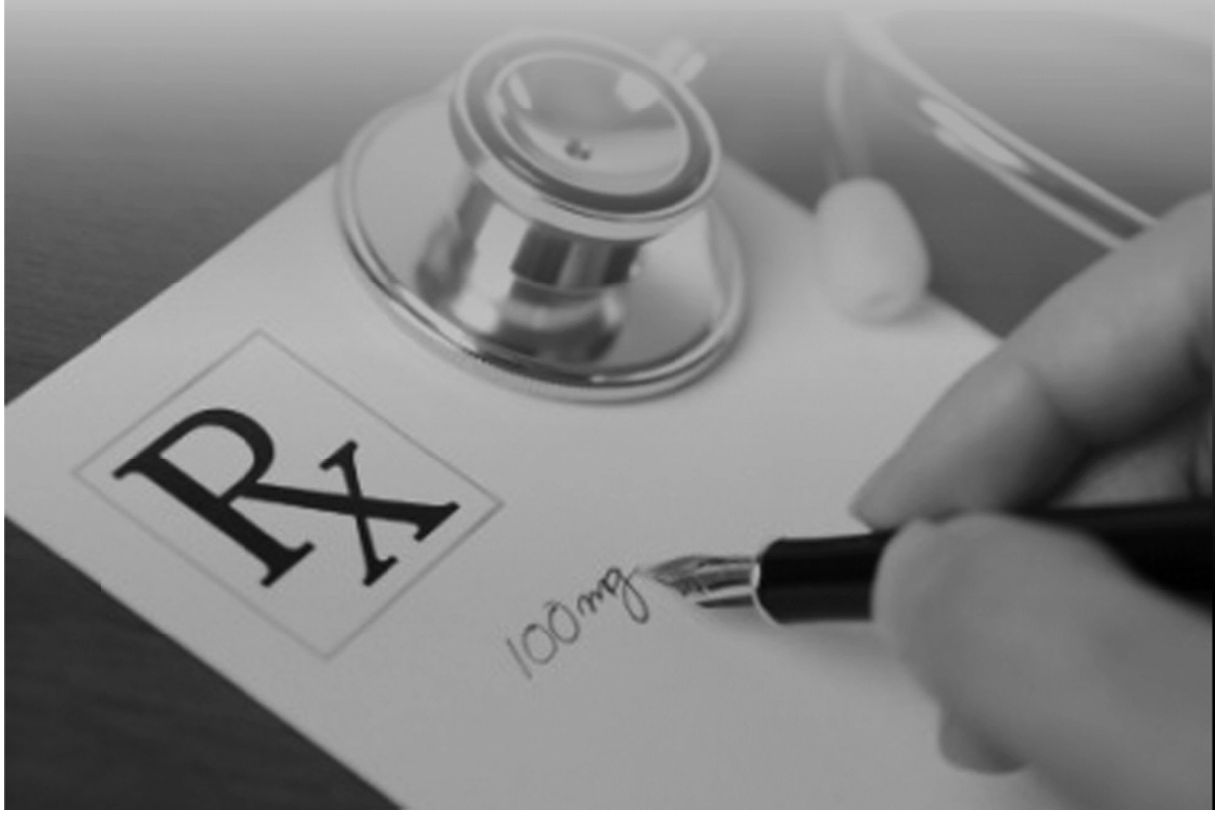
Chapter 1

General Principles



Chapter 1

General Principles

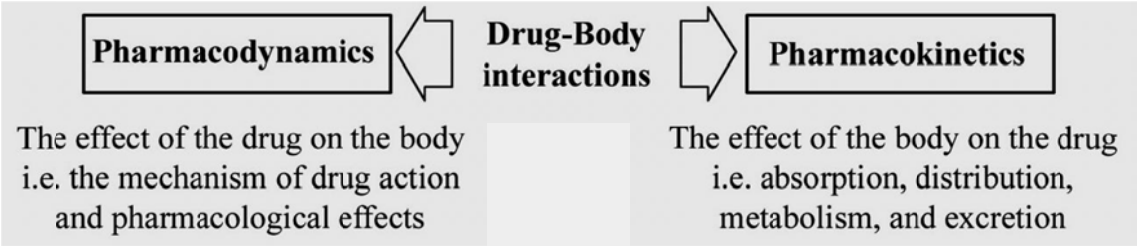
Introductory definitions

Medical pharmacology is a basic science. It the science dealing with small molecules used to prevent, diagnose, or treat diseases.

Clinical pharmacology is the science concerned with the rational, safe and effective use of drugs in humans. It combines elements of basic pharmacology with clinical medicine; in other words, it involves the complex interaction between the **drug** and the **patient**.

A drug is any chemical molecule that can interact with body systems at the molecular level and produce effect.

The drug-body interactions


Pharmacodynamics
Drug-Body interactions
Pharmacokinetics
The effect of the drug on the body i.e. the mechanism of drug action and pharmacological effects
The effect of the body on the drug i.e. absorption, distribution, metabolism, and excretion

Part 1: Pharmacodynamics (Mechanism of drug action)

Pharmacodynamics is summarized as what a drug does to the body; a drug may produce its effects through:

- **Interaction with body control systems** (regulatory proteins):
  - (a) Receptors
  - (b) Ion channels
  - (c) Enzymes
  - (d) Carrier molecules
- Direct chemical or physical mechanisms.
- Interaction with certain metabolic pathways.

A. RECEPTORS

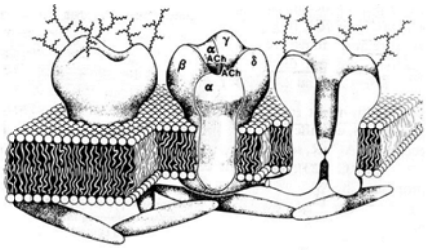
Receptors: they are protein macromolecules. When they combine with a drug, they may be activated or blocked.

Ligand: is any molecule that can combine with the receptors. A ligand that activates the receptor is called **agonist**. A ligand that blocks the receptor is called **antagonist.**

Affinity: it is the empathy of the receptor to the ligand. It determines *the number* of receptors occupied by the drug.

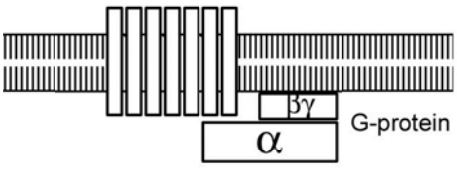
Types of receptors

- **Ion channel-linked receptors (direct ligand-gated ion channels):**

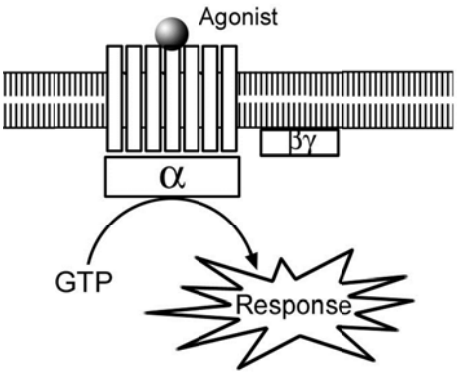


- The receptor is an ion channel consists of **5** transmembrane subunits (α_1, α_2, β, γ, δ).
- Binding of the agonist to the extracellular part of the receptor causes opening of the channel for a specific ion.
- The response of these receptors is very fast and their duration is very short.
- Examples:
  - *Nicotinic Ach receptors in the motor end-plate:* the ion channel opens for Na^+ ions in response to stimulation by Ach.
  - *The Gama aminobuteric acid (GABA) receptors in the brain:* the ion channel opens for Cl^- ions in response to stimulation by GABA.

- **G-protein-linked receptors:**



- The receptor consists of **7** membrane subunits.
- Binding of the agonist to the extracellular part of the receptor causes activation of intracellular G-protein.
- When the G-protein is activated, its α subunit binds to GTP to be phosphorylated and bring stimulatory or inhibitory response.
- Their response is slower than ion channel receptors but their duration is longer.

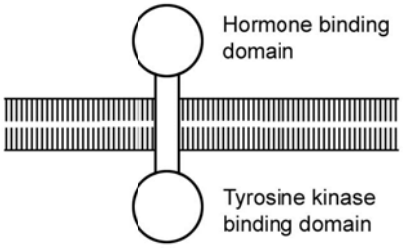


- **Stimulatory G-protein (Gs)** leads to increase *adenyl cyclase enzyme* → ↑ cAMP → activation of specific proteins (protein kinases). Examples of Gs-coupled receptors are the β1 and β2-adrenergic receptors.

- **Inhibitory G-protein (Gi)** leads to decrease *adenyl cyclase enzyme* → ↓ cAMP → inhibition of protein kinases. Examples of Gi-coupled receptors are the α2-adrenergic receptors and M2 muscarinic receptors.

- **Gq-coupled receptors:** they increase inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 increases free intracellular Ca^{2+}. Examples of Gq-coupled receptors are the α1-adrenergic receptors, M1 and M3 muscarinic receptors.

■ Tyrosine kinase (TK)-linked receptors:

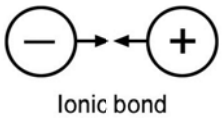


- The receptor consists of 2 large domains: an extracellular hormone-binding domain and an intracellular TK-binding domain connected by a transmembrane segment.
- Binding of the agonist to the hormone-binding domain causes activation of the intracellular domain to activate TK enzyme → activation of several proteins known as *"signaling proteins"*.
- Examples: *insulin receptors.*

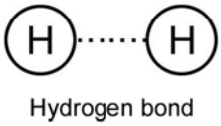
■ Intracellular receptors:

- They are located inside the cell either in the cytoplasm or **directly on the DNA**.
- They regulate transcription of genes in the nucleus or the mitochondria.
- Their agonist must enter inside the cell to reach them.
- They have two important features:
  - Their response is **slow** (time is required for synthesis of new proteins).
  - Their effects persist for **long time** after the agonist is removed.
- Examples: receptors for ***corticosteroids****, sex hormones, thyroxin, etc.*

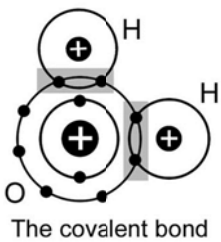
Types of drug-receptor bonds



■ **The ionic bond:**
It is an electrical attraction between two opposing charges. It is strong but reversible.



■ **The hydrogen bond:**
It is an attraction between two hydrogen bonds. It is weak and reversible.



■ **The covalent bond:**
Very strong and irreversible.
If occurred between drug and receptor, the receptor becomes permanently blocked.

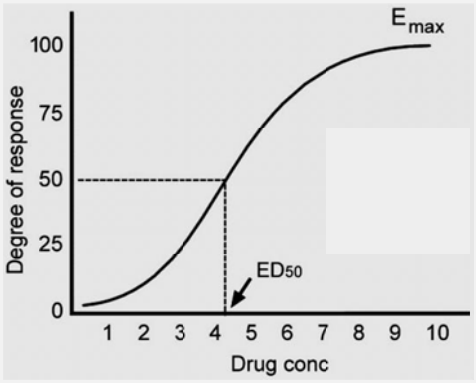
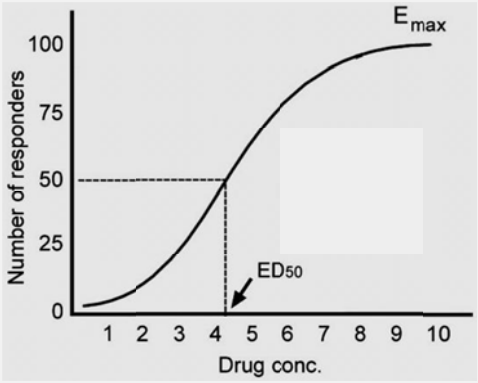
BIOLOGICAL RESPONSE TO DRUG-RECEPTOR BINDING (Dose-response relationship studies)

When a drug combines with a receptor, this may lead to one of the following:

- **Agonist effect:** means that the drug combines with the receptor and gives response.
- **Antagonist effect:** means that the drug combines with the receptor but gives **NO response,** and prevents the receptor from binding to another drug.

Agonist effect

According to the **"dose-response relationship curves"**, there are **2 types** of responses to drugs:

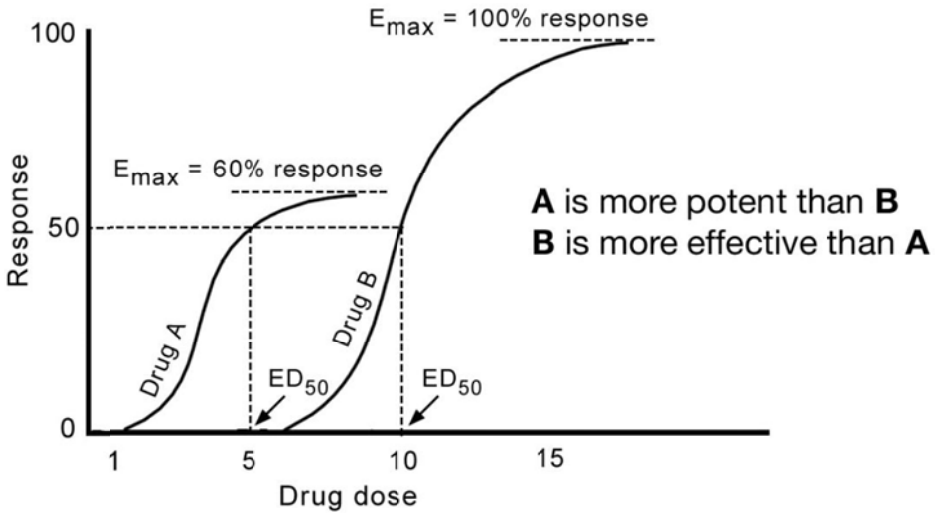
Graded response	Quantal response
– The response is increased **proportionally** to the dose of the agonist e.g. the response of the heart to adrenaline. – It is the response to **most** drugs. – The response could be tested in **one or more** animals.	– The response does not increase proportionally to the agonist but it is **all-or-none** response e.g. prevention of convulsions by antiepileptic drugs – It is response to **few** drugs. – The response could not be tested in one animal and must be tested in a **group** of animals.
	

Effectiveness and safety

- **Efficacy**

– It is the ability of a drug to produce response (effect) after binding to the receptor.
– It is measured by the **Emax** (the maximal response that a drug can elicit at full concentration):

- **Full agonist** is the drug that gives maximal response at full concentration (at full occupancy).
- **Partial agonist** is that agonist gives submaximal response even at full concentration i.e. never gives Emax

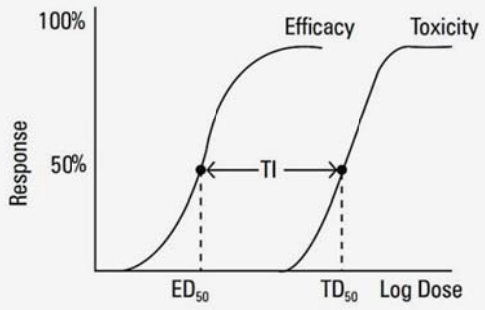


■ Potency

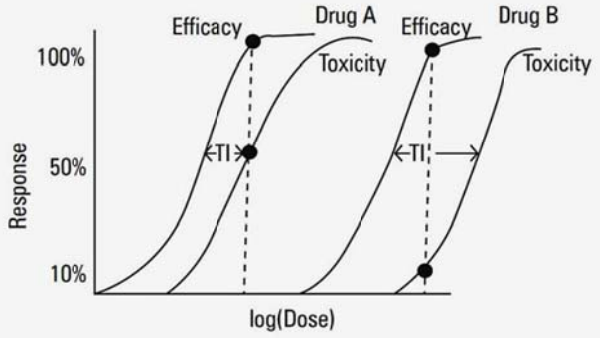
- **ED50 (Effective Dose)** is the dose of the drug that gives 50% of the Emax, or it is the dose that gives the desired effect in 50% of a test population of subjects.
- A drug that gives ED50 by smaller doses is described as **"potent"** drug.
- Potency of drugs is generally **less clinically important** than efficacy because you can increase the dose of a less potent drug to obtain the effect of a more potent one (provided that it is not toxic).

■ Safety

- **TD50 (Toxic Dose)** is the dose of the drug needed to cause a harmful effect in 50% of a test population of subjects.
- **LD50 (Lethal Dose)** is the dose needed to cause death in 50% of a test group of animals. It is experimental term that can be determined in animals.



The therapeutic index (TD_{50}/ED_{50}) is a measure of the margin of safety of a given drug

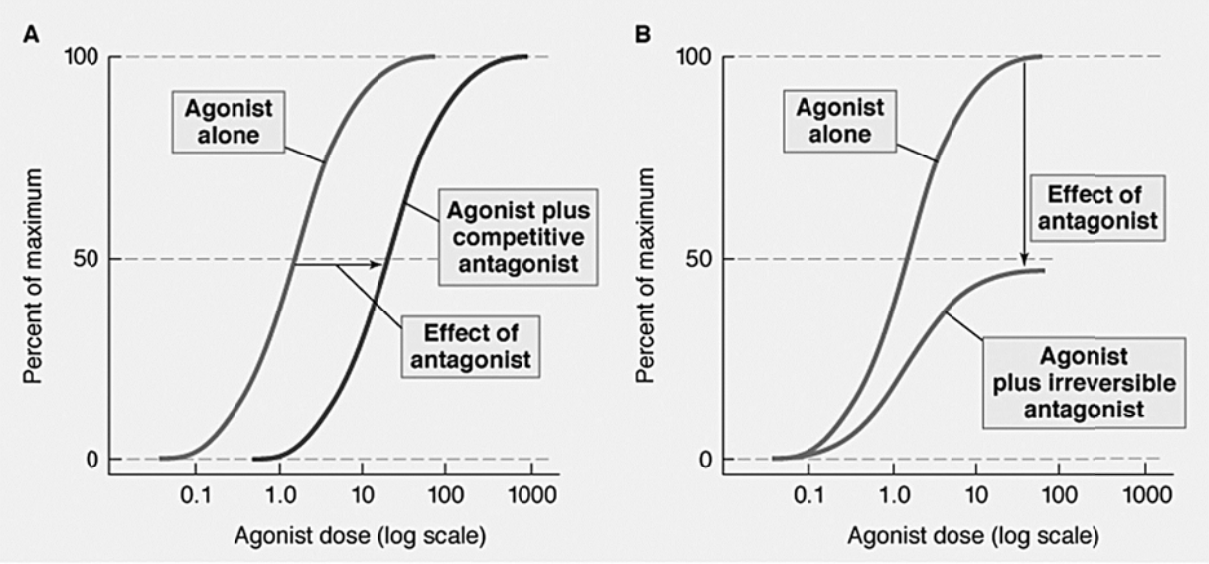


Drug A has a much narrower therapeutic index than Drug B. The dose of Drug A required to achieve a 100% therapeutic response will be toxic in 50% of patients. For Drug B, this is only 10%

- **Therapeutic index (TI) LD50/ED50:**
- It is the ratio between the LD50 and the ED50. It is a measure of safety; if there is a large difference between the dose of a drug that produces the desired effect and the dose that produces a toxic effect, it is said that the drug has a large TI.
- Drugs with high TI are more safe for clinical use, and *vice versa* (e.g. warfarin has a narrow TI and requires careful therapeutic monitoring).

Antagonist effect

- **Antagonist** is the ligand that combines with the receptor and **does not activate it**. It has no intrinsic activity, but may cause a pharmacological response by inhibiting the actions of endogenous substances or other drugs.
- If the antagonist binds to the same site of the agonist on the receptor, it is called **competitive antagonist**. If the antagonist binds to another site on the receptor, and prevented the action of the agonist, it is called **non-competitive antagonist**.
- **Competitive antagonism** may be **reversible** or **irreversible:**
  - **Reversible antagonist** makes **weak** bond with the receptor so as you can overcome the block by giving high doses of the agonist, and even you can get the maximal response in presence of the antagonist (i.e. surmountable effect). The duration of block is short because the antagonist can be easily washed off the receptors.
  - **Irreversible antagonist** makes **covalent** bond with the receptor so as you cannot overcome the block or get the maximal response by increasing the dose of the agonist (i.e. non-surmountable effect). The occupied receptors are permanently blocked, so the duration of block is long, and the body has to synthesize new receptors to regain the original state.



Reversible antagonism | Irreversible antagonism

Other types of drug antagonism

- **Chemical antagonism:** e.g. one **acidic** drug when added to a **basic** drug can cause precipitation of each other's

  Example: the addition of gentamycin (basic drug) to carpenicillin (acidic drug) in the same syringe causes chemical complex.

- **Physical antagonism:** antagonism between two drugs carrying opposite charges.

  Example: **protamine** is used for treatment of **heparin** overdose because protamine carries **+ve** charge while heparin carries **–ve** charge. One mg of protamine can neutralize 100 units of heparin.

- **Physiological antagonism:** antagonism between two drugs producing opposite effects by activation of different receptors.

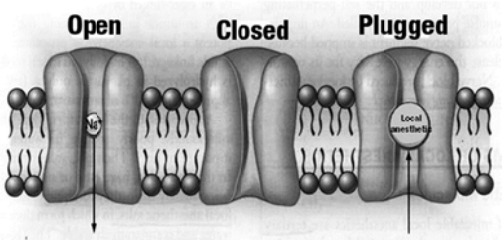
  Example: **adrenaline** is the physiological antagonist of **histamine** because while histamine causes hypotension and bronchoconstriction through activation of histamine H_1 receptors, adrenaline causes hypertension and bronchodilatation through activation of adrenergic α & β receptors respectively.

- **Pharmacokinetic antagonism:** (see drug interactions).

– One drug may **prevent absorption** of another drug e.g. antacids ↓ absorption of iron & aspirin.
– One drug may **increase metabolism** of another drug e.g. rifampicin induces hepatic enzymes and ↑ metabolism of oral contraceptive pills.
– One drug may ↑ **excretion** of another drug e.g. NaHCO3 cause alkalinization of urine and ↑ excretion of acidic drugs like **aspirin**.

B. ION CHANNELS

How drugs could modulate ion channels?



- Physical block: e.g. blocking of Na^+ channels by local anesthetics.
- The ion channel may be part of the receptor e.g. ion channel-linked receptors.
- The ion channel may be modulated by G-protein linked receptors.
- Ion channels may be modulated by intracellular ATP e.g. ATPase sensitive K^+ channels in the pancreatic β cells, rise of intracellular ATP causes closure of pancreatic K^+ channels.

C. ENZYMES

How drugs could affect enzymes?

- The drug may act as a competitive inhibitor of the enzyme e.g. neostigmine on cholinesterase enzyme.
- The drug may act as irreversible inhibitor of the enzyme e.g. organophosphates on cholinesterase enzyme.
- The drug may act as a false substrate for the enzyme e.g. α-methyldopa is a false substrate for *dopa decarboxylase*.
- The drug may induce or inhibit hepatic microsomal enzymes activity (see later).

D. CARRIER MOLECULES

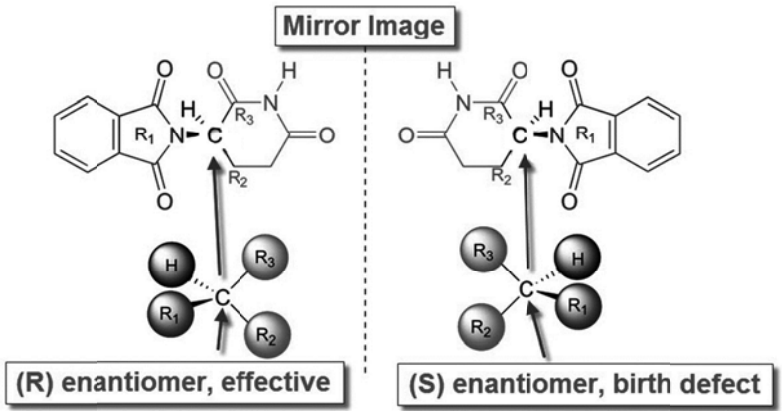
- These are small protein molecules that carry organic molecules across the cell membrane when they are too large or too polar.
- Drugs could affect carrier molecules by blocking their recognition site.

Part 2: Factors affecting dose-response relationship

A. FACTORS RELATED TO THE DRUG

1. Drug shape (stereoisomerism):

- Most drugs have multiple stereoisomers (enantiomers) (e.g. L-thyroxin and D-thyroxin). The receptor site is usually sensitive for one stereoisomer and not suitable for another, like the hand and the glove. This means that one isomer may be hundred times more potent than the other. In other instances one isomer is beneficial while the other is toxic.



- This phenomenon may explain how a single drug could act as agonist and antagonist (i.e. partial agonist) because many drugs are present in **"racemic mixtures"** rather than as pure isomers; or how one isomer is effective and the other isomer is toxic.

2. Molecular weight (MW):

- Most drugs have MW between 100-1000 Da. Drug particles larger than MW 1000 Da cannot be absorbed or distributed. They should be given parenterally.
- Drug particles larger than MW 1000 Da cannot cross placental barrier.

3. Time of drug administration (Chronopharmacology):

- Many body functions (e.g. liver metabolism, RBF, blood pressure, HR, gastric emptying time, etc.) have daily circadian rhythm. Some enzymes responsible for metabolism of drugs are active in the morning or evening.
- Also many diseases (e.g. asthma attacks, myocardial infarction, etc.) are circadian phase dependent.
- *Chronopharmacology* is the science dealing with tailoring drug medication according to the circadian rhythm of the body to get better response and/or to avoid possible side effects.
- Examples:
- Episodes of acute bronchial asthma are common at night due to circadian variation of cortisol and other inflammatory mediators, so it is better to give the anti-asthmatic medications in the evening.
- Blood pressure is at its peak during afternoon, so it is better to give the antihypertensive medications at morning.

4. Drug cumulation:

Cumulation occurs when the rate of drug administration exceeds the rate of its elimination (especially in patients with liver or renal disease). Some drugs are cumulative due to their slow rate of elimination e.g. digoxin.

5. Drug combination:

Drug combination is very common in clinical practice. When two or more drugs are combined together, one of the following may occur:

a) Summation or addition:

- Summation means that the combined effect of two drugs is *equal* to the sum of their individual effects (i.e. 1+1=2). It usually occurs between drugs having the same mechanism, for example, the use of two simple analgesics together.

b) Synergism and potentiation:

- Synergism means that the combined effect of two drugs is *greater* than the sum of their individual effects (i.e. 1+1=3). The two drugs usually have different mechanisms of action, for example, the use of *penicillin* with *aminoglycosides* to exert bactericidal effect.

- Potentiation is similar to synergism but, in potentiation, the effect of one drug itself is greatly increased by intake of another drug without notable effect (i.e. 1+0=2), for example, *Phenobarbitone* has no analgesic action but it can potentiate the analgesic action of *aspirin*.

c) Antagonism:

One drug abolishes the effect of the other i.e. 1+1=0 (see before).

B. FACTORS RELATED TO THE PATIENT

1. Age, sex, and weight.

2. Pathological status:

Liver or kidney diseases significantly alter the response to drugs due to altered metabolism. Also the failing heart is more sensitive to digitalis than the normal heart.

3. Pharmacogenetic factors (idiosyncrasy):

It is abnormal response to drugs due to genetic abnormality in drug metabolism. These are some examples:

Examples of heritable conditions causing EXAGGERATED drug response:

a) Pseudocholinestrase deficiency:

Succinylcholine is a neuromuscular blocker metabolized by *pseudo-cholinestrase* enzyme. Some individuals with deficient PsChE, when they take succinylcholine, severe muscle paralysis occurs due to lack of succinylcholine metabolism, and may lead to death from respiratory paralysis (*succinylcholine apnea)*.

b) Glucose-6-phosphate dehydrogenase (G6PD) deficiency:

- G6PD is the most common human enzyme defect. G6PD enzyme catalyzes the reduction of NADP+ into NADPH which maintains glutathione in the RBCs in its reduced form. Reduced glutathione keeps Hb in the reduced (ferrous) form and prevent formation of methemoglobin and cell membrane injury (hemolysis) by oxidizing drugs.
- Individuals with deficiency of G6PD may suffer acute hemolysis if they are exposed to oxidizing drugs e.g. nitrates, antimalarial drugs, and others.

c) Thiopurine methyltransferase (TPMT) deficiency:

- Thiopurine methyltransferase (TPMT) is an enzyme that methylates thiopurine anticancer drugs (e.g. 6-mercaptopurine and 6-thioguanine) into less toxic compounds.

- Genetic deficiency in TPMT leads to increased conversion of parent thiopurine drugs into more toxic compounds, leading to severe myelotoxicity and bone marrow suppression which may be fatal.
- TPMT deficiency prevalence is 1:300. Screening for TPMT deficiency is necessary in patients treated by thiopurine anticancer drugs.

d) Acetylator phenotypes:

Many drugs are metabolized in the liver by acetylation (e.g. **isoniazid)**. Acetylation reaction is under genetic control and people can be classified according to their rate of acetylation into **rapid** and **slow** acetylators:

- In rapid acetylators: excessive isoniazid toxic metabolites accumulate in the liver causing *hepatocellular necrosis*.
- In slow acetylators: isoniazid accumulates in peripheral tissues causing *peripheral neuropathy* due to interference with pyridoxine metabolism, (so pyridoxine "vit B6" is added to isoniazid therapy to prevent neurotoxicity).
- Some drugs that are metabolized by acetylation can cause systemic lupus erythematosis-like syndrome (SLE) in slow acetylators (see box).

Drug-induced SLE like syndrome

Hydralazine (+++)
Procainamide (++)
Isoniazid (+)
Quinidine (+)
Phenytoin (+)

Examples of heritable conditions causing DECREASED drug response:

a) Resistance to coumarin (warfarin) anticoagulants:

- In normal individuals, warfarin anticoagulant acts by inhibiting the enzyme *vit K epoxide reductase* responsible for reduction of the oxidized vit K (inactive) to its reduced form (active).
- Some individuals have another variant of this enzyme making them needing 20 times the usual dose of coumarin to get the response.

b) Resistance to vit D (vit D-resistant rickets):

Children with *vit D-resistant rickets* need huge doses of vit D to be treated.

c) Resistance to mydriatics:

Dark eyes are genetically less responsive to the effect of **mydriatics**.

4. Hyporeactivity to drugs:
(Tolerance; tachyphylaxis; drug resistance)

Tolerance means progressive decrease in drug response with successive administration. The same response could be obtained by higher doses. It occurs over long period. **Tachyphylaxis** is an acute type of tolerance that occurs very rapidly.

Mechanism of tolerance:

- ***Pharmacodynamic tolerance:*** may occur due to:
  - Receptor desensitization: prolonged exposure to the drug leads to slow conformational changes in the receptors by which the receptor *shape* becomes no longer fitted well with the drug.
  - Receptor down-regulation: prolonged exposure to the drug leads to decrease *number* of the functional receptors.
  - Exhaustion of mediators: e.g. depletion of catecholamines by amphetamine.
- ***Pharmacokinetic tolerance:***
  - Due to ↑ metabolic degradation of a drug by induction of hepatic enzymes e.g. with chronic administration of ethanol.
- ***Behavioral tolerance:***
  - It occurs by a drug independent learning of the brain how to actively overcome a certain drug-induced effect through practice e.g. with psychoactive drugs.

5. Hyperreactivity to drugs:
(Rebound and withdrawal effect)

Rebound effect: is recurring of symptoms in exaggerated form when a drug is suddenly stopped after a long period of administration.

Mechanism: prolonged administration of the **antagonist** leads to up-regulation (increase number) of receptors. When the antagonist is suddenly stopped, severe reaction occurs e.g. severe tachycardia and arrhythmia occurs after sudden stopping of beta-blockers.

Withdrawal effect (syndrome) is recurring of symptoms in exaggerated form plus addition of new symptoms when a drug is suddenly stopped e.g. withdrawal effects that occur after sudden stopping of opioids in opioid addicts.

N.B. Some examples of drugs should not be stopped suddenly:

Drug		Sudden withdrawal can lead to:
Beta-blockers	:	Severe tachycardia, arrhythmia, and even myocardial infarction.
Clonidine	:	Severe hypertension (hypertensive crisis).
Cimetidine	:	Severe hyperacidity and even peptic ulceration.
Corticosteroids	:	Acute Addisonian crisis.
Morphine	:	Withdrawal symptoms (see CNS).
Warfarin	:	Thrombotic catastrophes

Part 3: Clinical pharmacokinetics

Definition: it is the journey of the drug inside the body. It includes 4 processes:

Absorption **D**istribution **M**etabolism **E**xcretion

ABSORPTION OF DRUGS

Definition: it is the passage of drug from the site of administration **t**o the plasma.
The main routes of administration: oral, sublingual, rectal, inhalation, injection, etc.

Factors affecting drug absorption:

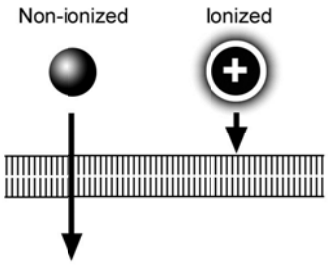
A. Factors related to the drug

- Molecular size: small molecules are absorbed than large molecules.
- Dose: absorption increases with increasing the dose (up to limit).
- Drug formulations: e.g. sustained-release tablets are slow in absorption.
- Local effects of the drug: e.g. drugs producing VC ↓ their own absorption.
- Drug combination: e.g. vit C ↑ absorption of iron.
- Lipid solubility, drug ionization, and the pKa of the drug.

B. Factors related to the absorbing surface:

- Route of administration: i.v. route is the fastest while rectal is the slowest.
- Integrity of the absorbing surface: may ↑ or ↓ absorption.
- Local blood flow: ischemia ↓ absorption.
- Specific factors: e.g. apoferritin system for iron, etc.

The pKa and drug ionization



Principles

- Ionized (polar; charged) drugs are **poorly** absorbed, while unionized (non-polar, non-charged) drugs are **more** absorbed.
- Most drugs are weak acids or **b**ases. They become ionized or non-ionized according to the **pH** around them.
- Acidic drugs (e.g. aspirin) are more ionized in alkaline pH and *vice versa.*
- Basic drugs (e.g. amphetamine) are more ionized in acidic pH and *vice versa*.
- **pKa of a drug: is the pH at which 50% of the drug is ionized and 50% is non-ionized**. *(Where p = inverse log; Ka = association/dissociation constant).*

Example of pH variation and drug kinetics with aspirin:

Aspirin is an acidic drug; its **pKa = 3.5**
The pH of the stomach is **1.5** The pH of the intestine is **8.5**

►When aspirin is put in the stomach:

- Aspirin is acidic drug and becomes more absorbable in acidic pH.
- Log (Unionized /Ionized)* = pKa – pH = 3.5 – 1.5 = 2 (log 2 =10^2).
- This means that the ratio of unionized: ionized = 100/1 (or accurately 0.99 parts are absorbed and 0.01 parts are non-absorbed).

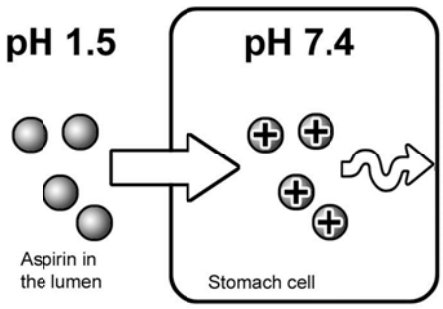
►When aspirin is put in the intestine:

- Aspirin is acidic drug and becomes less absorbable in alkaline pH.
- Log (Unionized/Ionized)* = pKa – pH = 3.5 – 8.5 = – 5 (log -5 =10^{-5}).
- This means that the ratio of unionized/ionized = 1/100000 (or accurately 0.00001 parts are absorbed and 0.99999 parts are non-absorbed).

***N.B.** The above rule applies only to acidic drugs like aspirin. For basic drugs, the ratio would be reversed.

►Ion trapping of aspirin:

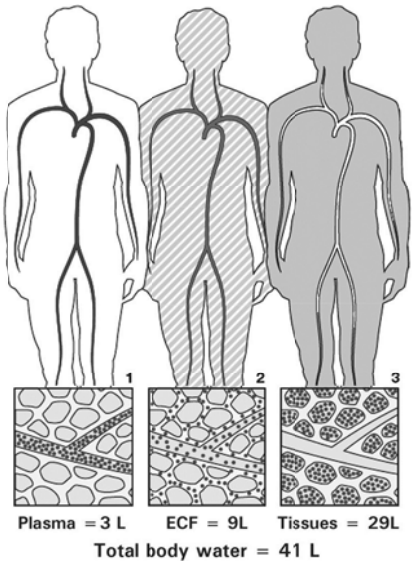
In the stomach, aspirin is more absorbable into stomach cells but once entered the cells, the pH changes from 1.5 outside to 7.4 inside the cell. So aspirin becomes ionized inside the cells and can't diffuse outside them again → gastric ulcer.



Clinical significance of pKa

- Knowing the site of drug absorption from the GIT (see principles).
- Treatment of drug toxicity:
  - Toxicity with acidic drugs (e.g. aspirin) could be treated by alkalinization of urine, which renders this drug more ionized in urine and less reabsorbable.
  - Toxicity with basic drugs (e.g. amphetamine) could be treated by acidification of urine, which renders this drug more ionized in urine and less reabsorbable.
- Ion trapping in breast milk:
  - The pH of the breast milk is 7 i.e. it is considered acidic in relation to plasma (pH 7.4).
  - Basic drugs (with pKa > 7.2) tend to be ionized, and thus trapped, inside breast milk more than acidic drugs; hence, the milk/plasma ratio (M/P ratio) would be high.

DISTRIBUTION OF DRUGS



Sites of drug distribution

- Plasma: 3 liters
- Extracellular water: 9 liters
- Intracellular water: 29 liters

Volume of distribution (Vd)

Definition: The apparent volume of water into which the drug is distributed in the body after distribution equilibrium.

Calculation:

$$Vd = \frac{\text{Total amount of the drug in the body}}{\text{Plasma conc of the drug (after distribution equilibrium)}} \text{ L}$$

Clinical significance:

- Determination of the **site of drug distribution** e.g.:
  - A total Vd < 5 L: means that the drug is confined to the vascular compartment and can be removed by dialysis.
  - A total Vd 5-15 L: means that the drug is restricted to the ECF.
  - A total Vd > 41 L: means that the drug is highly bound to tissue proteins and cannot be removed by dialysis.
- Calculation of **the total amount of drug in the body** by single measurement of plasma concentration (from the equation).
- Calculation of the **loading dose** (LD) needed to attain a desired plasma concentration (Cp): LD = Vd x Cp.
- Calculation of **drug clearance:**

$$\text{Clearance (Cl)} = \frac{0.693 \times Vd}{\text{Half-life } (t_{1/2})}$$

Binding of drugs to plasma proteins

- Most drugs when introduced into the body are bound to plasma proteins.
- Albumin: the most important plasma protein and it can bind –ve or +ve charged drugs.

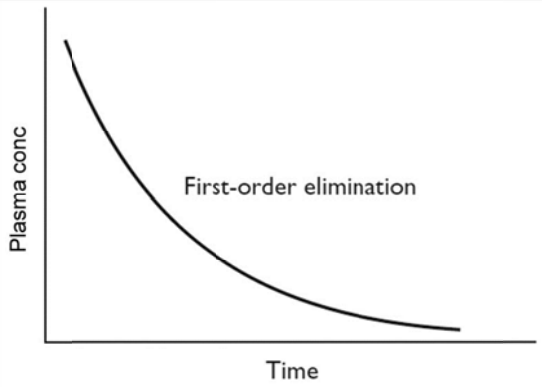
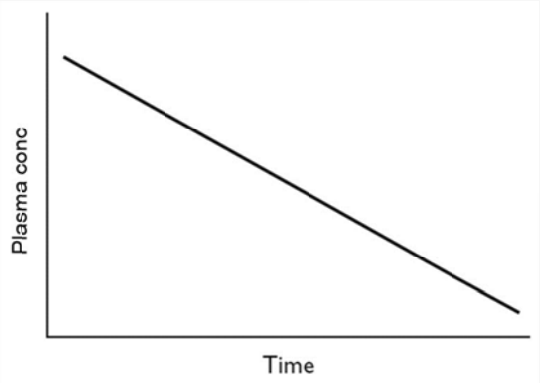
Clinical significance:

- The pharmacological effect of the drug is related only to its **free part** not to its bound part (the bound part acts only as a reservoir from which the drug is slowly released).

- Binding of drugs to plasma proteins **prolongs** their effects.
- When the drug has **high plasma protein binding** (e.g. 99% for warfarin), the free part that exerts the pharmacologic effect is 1%. Any small displacement of the bound part by another drug (say for example another1% is displaced) can lead to dramatic toxicity (doubles the amount of the free part in plasma).
- Many **disease states** (e.g. chronic liver disease, pregnancy, renal failure) can affect the level of albumin and the nature of plasma proteins, thus causing serious problems with some drugs.

EXCRETION AND ELIMINATION OF DRUGS

Elimination of drugs may follow one of 2 processes (orders):

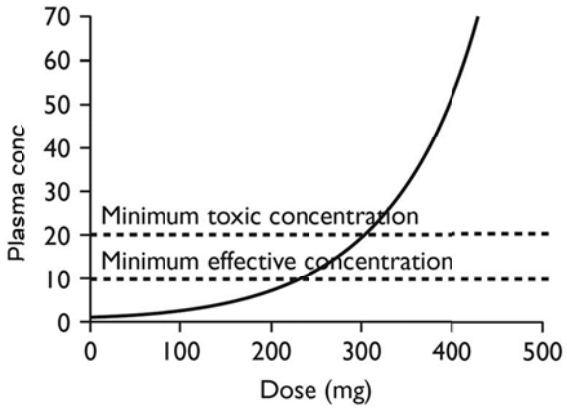
First-order elimination	Zero-order elimination
	
- Occurs to **most** drugs. - Constant **ratio (%)** of the drug is eliminated per unit time i.e. the rate of elimination is **proportional** to plasma concentration. The higher the concentration, the greater the rate of elimination. - Elimination **does not** depend on **saturable enzyme** system. - The $t_{1/2}$ of the drug is constant. - Drug cumulation is not common	- Occurs to **limited** number of drugs. - Constant **amount** of the drug is eliminated per unit time i.e. the rate of elimination is **not proportional** to plasma concentration. A familiar example is ethanol, concentrations of which decline at a constant rate of approximately 15 mg/100 mL/h. - Elimination depends on **saturable enzyme** system. - The $t_{1/2}$ of the drug is not constant. - Drug cumulation is common

Examples of drugs eliminated by zero-order: prednisolone, theophylline.

N.B. Some drugs are eliminated by first-order elimination in **low doses** and by zero-order elimination in **high doses** e.g. aspirin and phenytoin.

Clinical significance of zero-order elimination:

- Modest change in drug dose may produce unexpected toxicity.
- Elimination of drugs or attainment of Cpss takes long time.
- Changes in drug formulation may produce adverse effects.
- Drug cumulation and interactions are common.



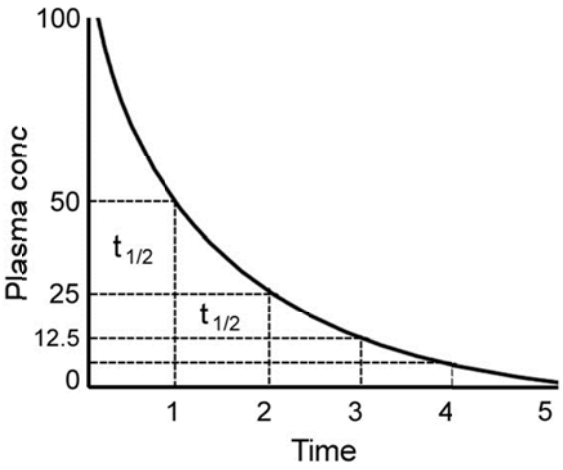
Elimination half-life ($t_{1/2}$)

Definition: It is the time taken for the concentration of a drug in blood to fall half to its original value.

Calculation:

- From the plasma concentration versus time curve.
- From the equation:

$$\text{Clearance (Cl)} = \frac{0.693 \times Vd}{\text{Half-life } (t_{1/2})}$$



Clinical significance:

- Determination of **inter-dosage interval:** drugs are given every $t_{1/2}$ to avoid wide fluctuations of the **peak** level (the highest plasma concentration of the drug) and **trough** level (the lowest plasma concentration).
- **Time-course of drug accumulation:** if a drug is started as a constant infusion, the Cp will accumulate to approach steady-state after 4-5 $t_{1/2}$.
- **Time-course of drug elimination:** If a drug is stopped after an infusion, the Cp will decline to reach complete elimination after 4-5 t1/2.
- Drugs having long $t_{1/2}$ could be given **once daily** to improve patient **compliance.**

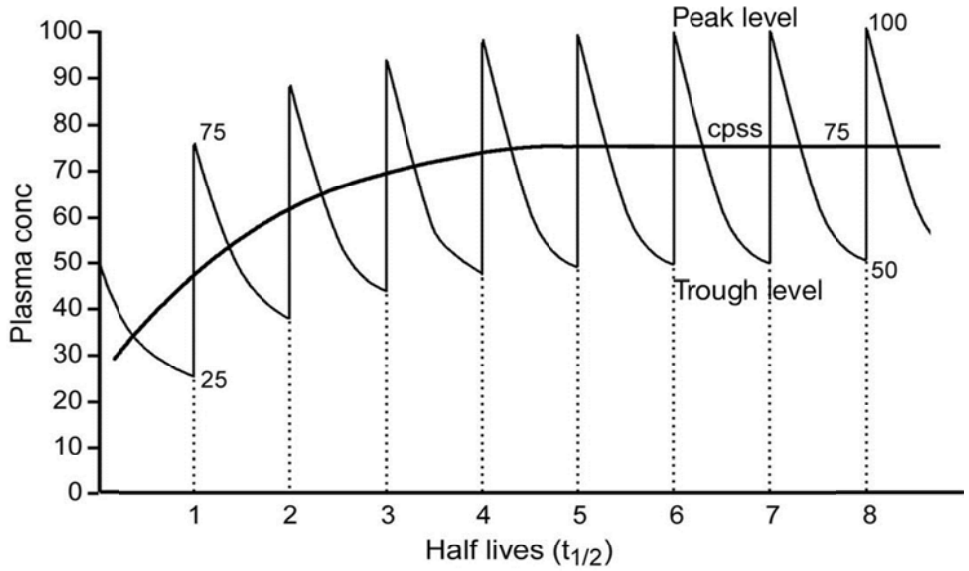
Steady-state plasma concentration (Cpss)

Definition: the steady level of drug in plasma achieved when the rate of administration equals the rate of elimination.

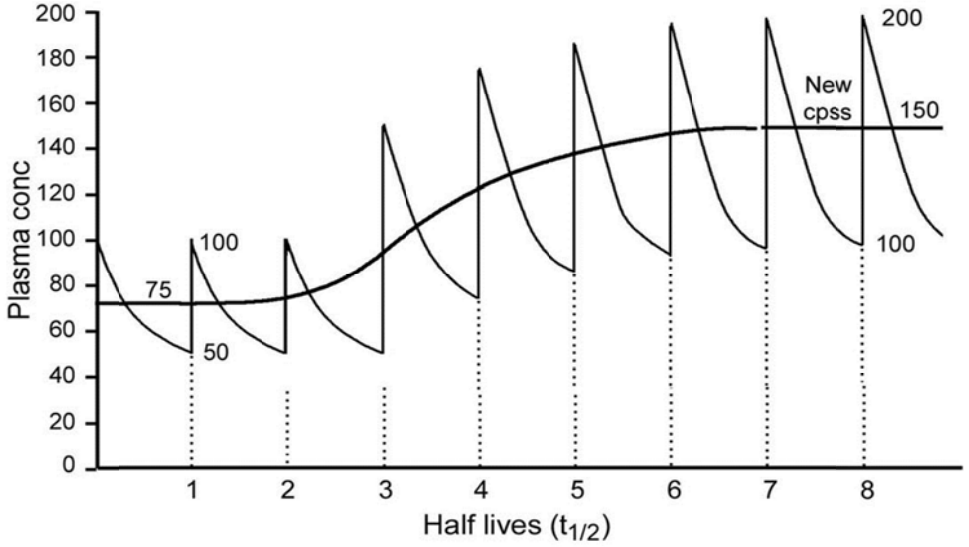
The rule of 5:

- The Cpss is reached after 4-**5** $t_{1/2.}$

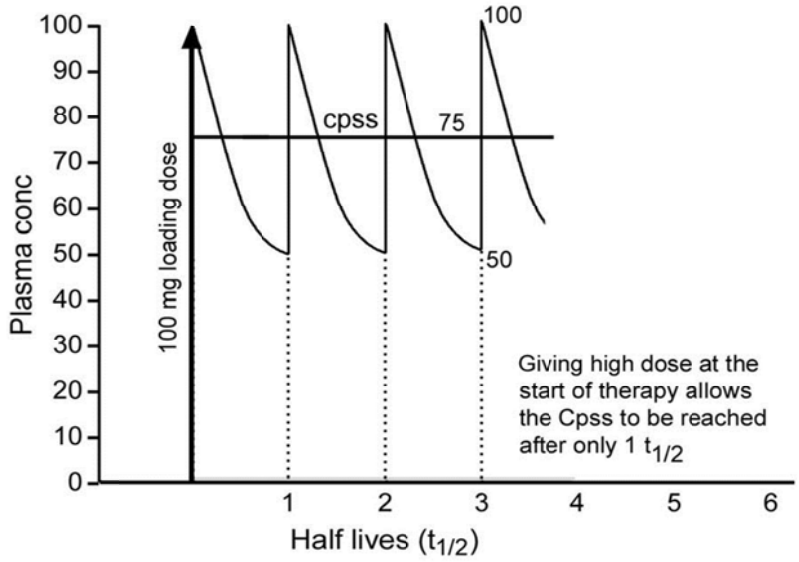
- If we changed the dose, the new Cpss is reached after 4-**5** $t_{1/2.}$
- If dosing stops, complete elimination of drug from plasma occurs after 4-**5** $t_{1/2.}$



Cpss is reached after 5 $t_{1/2}$



New Cpss is reached after 5 $t_{1/2}$



Therapeutic drug monitoring (TDM)

Definition: monitoring of serum drug concentrations to optimize drug therapy.

- Serum drug samples are usually taken when the drug has reached the CPSS (e.g. at the trough level, just before the next dose).
- TDM can be done by monitoring drug effect rather than concentration e.g. in warfarin therapy, TDM is done via monitoring the INR (see blood).

Clinical significance:

- **To avoid toxicity in the following situations:**
  - Drugs with a low 'therapeutic index' e.g. lithium, digoxin, and warfarin.
  - Presence of disease states (e.g. liver or renal dysfunction) that can affect the drug's pharmacokinetics.
- **To improve efficacy** of drugs having pharmacokinetic problems e.g. phenytoin and other drugs with non-linear kinetics.
- **Differentiation between** drug resistance and patient non-compliance.

Clearance as a channel of elimination

Definition: plasma clearance of a substance means the volume of plasma cleared from this substance per minute.

Calculation:

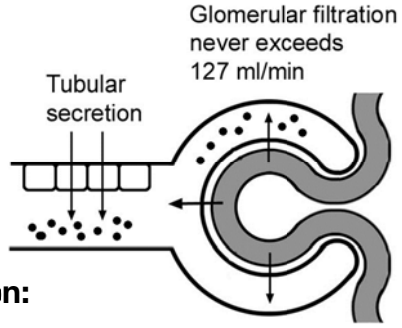
$$\text{Clearance (Cl)} = \frac{0.693 \times Vd}{\text{Half-life } (t_{1/2})}$$

Clinical significance of renal clearance:

If the drug is cleared by the kidney, clearance can help to determine whether this drug is eliminated by renal **filtration** or **secretion:** a drug that is eliminated only by *filtration* cannot exceed 127 ml/min. If clearance > 127 ml/min → the drug is eliminated also by *tubular secretion*.

Routes of elimination:

- Kidney (the major route).
- Bile and liver.
- Lungs, intestine, milk, saliva and sweat.



Clinical importance of knowing the route of elimination:

- Help to adjust the dose to avoid cumulation.
- Avoid drugs eliminated by a diseased organ.
- Targeting therapy: e.g. drugs eliminated by the lung could be used as expectorants.

METABOLISM OF DRUGS (biotransformation)

- The **liver** is the major site of drug metabolism but other organs can also metabolize drugs e.g. kidney, lungs, and adrenal glands.
- Many lipid soluble drugs must be converted into a **water-soluble form** (polar) to be excreted.
- Some drugs are not metabolized at all and excreted unchanged (**hard drugs**).
- **Metabolism of drugs may lead to:**
  - Conversion of **active** drug into **inactive** metabolites → termination of drug effect.
  - Conversion of **active** drug into **active** metabolites → prolongation of drug effect e.g. codeine (active drug) is metabolized to morphine (active product).
  - Conversion of **inactive** drug into **active** metabolites (**prodrugs**) e.g. enalapril (inactive drug) is metabolized to enalaprilat (active metabolite).
  - Conversion of **non-toxic** drug into **toxic** metabolites (e.g. paracetamol is converted into the toxic product *N*-acetylbenzoquinone).

Biochemical reactions involved in drug metabolism

The drug must enter **phase I** of chemical reactions be excreted as water-soluble compound. If the drug is not liable to conversion into water-soluble compound by phase I, it must enter **phase II** to increase solubility and enhance elimination.

Phase I reactions

- Phase I reactions include **oxidation, reduction,** and **hydrolysis**.
- Enzymes catalyzing phase I reactions include cytochrome P450, aldehyde and alcohol dehydrogenase, deaminases, esterases, amidases, and epoxide hydratases.
- The majority of phase I reactions is done by the **cytochrome P450** (CYP450) enzyme system located primarily inside membranous vesicles *(microsomes)* on the surface of the smooth endoplasmic reticulum of parenchymal liver cells. CYP450 activity is also present in other tissue e.g. kidney, testis, ovaries and GIT.

- Although this class has more than 50 enzymes, six of them metabolize 90% of drugs. The most important subfamily is CYP3A4 which is responsible for metabolism of over 50% of drugs.
- **Genetic polymorphism** of several clinically important CYP450 enzymes is a source of variability of drug metabolism in humans.
- Drugs may be metabolized by only one CYP450 enzyme (e.g. metoprolol by CYP2D6) or by multiple enzymes (e.g. warfarin).
- Some drugs and environmental substances can **induce** (increase activity) or **inhibit** certain CYP450 enzymes leading to significant drug interactions.
- Other examples of **non-microsomal oxidation** include xanthine oxidase (converts xanthine to uric acid) and monoamine oxidase (MAO) (oxidizes catecholamines and serotonin). Only the microsomal enzymes are subjected to induction or inhibition by drugs.

Microsomal enzyme induction	Microsomal enzyme inhibition
▪ Microsomal inducers ↑ rate of metabolism of some drugs leading to ↓ their serum levels and therapeutic failure. ▪ Induction usually requires prolonged exposure to the inducing drug.	▪ Microsomal inhibitors ↓ rate of metabolism of some drugs leading to ↑ their serum levels and toxicity. ▪ Enzyme inhibition can occur after short period of exposure to the inhibiting drug.
▪ Examples of inducing agents: phenytoin, phenobarbitone, carbamazepine, rifampicin, smoking, chronic alcohol intake, St John's Wort,	▪ Examples of inhibiting agents: macrolide antibiotics (e.g. erythromycin), ciprofloxacin, cimetidine, ketoconazole, ritonavir, grapefruit juice.
▪ Clinical examples: – Rifampicin accelerates metabolism of contraceptive pills leading to failure of contraception. – Phenytoin accelerates metabolism of cyclosporine-A leading to graft rejection.	▪ Clinical examples: – Ciprofloxacin inhibits metabolism of warfarin (anticoagulant) leading to accumulation of warfarin and bleeding. – Erythromycin inhibits metabolism of theophylline leading to toxicity of theophylline (cardiac arrhythmia).

Phase II reactions (conjugation)

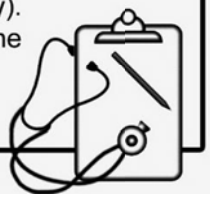
- It involve coupling of a drug or its metabolite to water-soluble substrate (usually glucuronic acid) to form water-soluble conjugate.
- **Glucuronyl transferase** is a set of enzymes that is responsible for the majority of phase II reactions. This set of enzymes is also located **inside liver**

microsomes and is the only phase II reaction that is **inducible by drugs** and is a possible site of drug interactions e.g. phenobarbital induces glucuronidation of thyroid hormone and reduces their plasma levels.

- Some glucuronide conjugates secreted in bile can be hydrolyzed by intestinal bacteria and the free drug can be reabsorbed again (enterohepatic circulation), this can extend the action of some drugs.
- Other examples of **non-glucurounide conjugation** reactions include sulphate conjugation (steroids), glycine conjugation (salicylic acid), and glutathione conjugation (ethacrynic acid).

N.B. Breakthrough pregnancy!!!

- Contraceptive pills contain estrogen, which is metabolized by glucuronide conjugation and excreted in bile as conjugate.
- Intestinal bacteria hydrolyze this conjugate to form free estrogen again which is reabsorbed and attain long duration of action (so contraceptive pills are given once daily).
- If the woman took contraceptive pills with broad-spectrum antibiotics (kills the intestinal bacteria), estrogen will lose its long duration of action and pregnancy can occur.

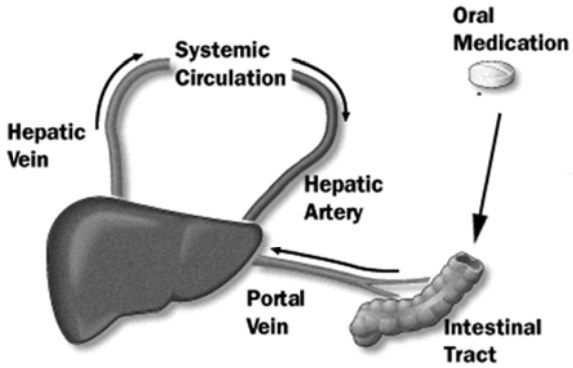


First-pass metabolism (pre-systemic elimination)

Definition: metabolism of drugs at the site of administration before reaching systemic circulation e.g. the liver after oral administration, the lung after inhalation, the skin after topical administration, etc.

Hepatic first-pass metabolism:

- Complete: lidocaine.
- Partial: propranolol, morphine, nitroglycerine
- None: atenolol and mononitrates



How to avoid?

- By increasing the dose of the drug.
- By giving the drug through other routes e.g. sublingual, inhalation, or i.v.

Bioavailability

Definition: it is the fraction of the drug become available for systemic effect after administration. The bioavailability of drugs given i.v. is 100%.

Factors affecting bioavailability:

- Factors affecting absorption.
- Factors affecting metabolism.
- First-pass metabolism.

Part 4: Adverse drug reactions (ADR)

An ADR is any response to a drug which is noxious, unintended, and occurs at doses used in man for prophylaxis, diagnosis or therapy.

Predisposing factors:

- Multiple drug therapy.
- Extremes of age: due to age related changes in pharmacokinetics and dynamics.
- Associated disease: e.g. impaired renal or hepatic function.
- Genetics: can affect the pharmacokinetics.

Classification:

Type A (Augmented):

These reactions are predictable from the known pharmacology of the drug. They may result from an **exaggerated response** (e.g. hypotension from an antihypertensive) or **non-specificity** (e.g. anticholinergic effects with tricyclic antidepressants).

Prevention

- Take a careful history for predisposing factors.
- Use the smallest dose of the drug adequate for the desired effect.
- Adjust dosage to therapeutic end-points, e.g. blood pressure or INR.
- Adjust dosage to optimum plasma concentrations, e.g. digoxin.
- Adjust dosage in relation to renal function, hepatic function, or other drugs.

Type B (Bizarre):

These are less common, less predictable, and may be severe. **Examples are:**

- Immunologic: penicillin allergy
- Genetic: haemolysis in G6PD deficiency
- Disease: amoxycillin rash in glandular fever
- Idiosyncratic: malignant hyperpyrexia in anesthesia.

Prevention

- Take a careful drug history, especially of allergies

- Family history: allergies or genetic disease
- Avoid drugs susceptible to ADRs in particular disease states, e.g. clozapine in bone marrow depression.

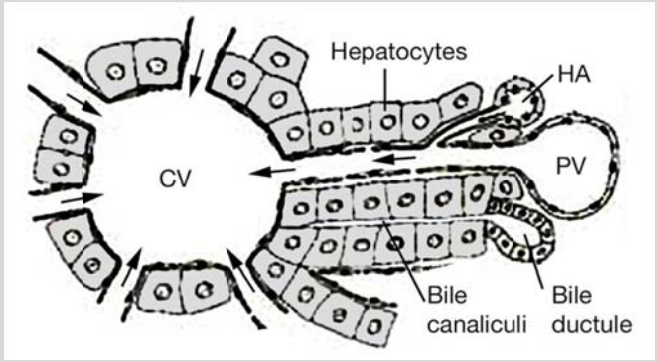
Type A (Augmented)	Type B (Bizarre)
– Predictable	– Unpredictable
– Dose-dependent	– Dose-independent
– High incidence	– Low incidence
– May respond to dose adjustment	– Generally need to stop the drug

Drug-induced liver injury (DILI)

DILI accounts for up to 10% of all adverse drug reactions and may be fatal.
It may be classified into:

- According to **time course**: acute or chronic.
- According to **mechanism**: dose-dependent, idiosynchratic, or immune mediated
- According to **histological finding**: hepatocellular, cholestatic, or mixed picture.

Hepatocellular (cytotoxic) DILI	Cholestatic DILI
Features: – The drug or its metabolites affects parenchymal liver cells leading to cell necrosis and initiation of inflammatory process. – It may be spotty, zonal, or diffuse. – Clinically it resembles viral hepatitis with ↑ ALT and AST.	**Features:** – The drug or its metabolites affect the biliary canaliculi leading to narrowing or destruction of biliary passages. – Clinically it resembles obstructive jaundice with pruritus and ↑ALP.
Common drugs: Paracetamol – methyldopa – amiodarone – isoniazid – valproic acid	**Common drugs:** Chloropromazine – sulfonylureas – oral contraceptive pills – anabolic steroids – macrolides – co-amoxiclav



ADR on pregnancy

Key facts:

- Fetal birth defects represent 2-3% of all births, the majority of which are related do drugs.
- Some fetal defects may be impossible to identify, or can be delayed e.g. the use of diethylstilbesterol (estrogenic compound) during pregnancy is associated with development of adenocarcinoma of girls' vagina at teen age.
- **Three factors** determine the risk of teratogenicity: **dose** of the drug; **duration** of administration; and **stage** of pregnancy.
- Most drugs with a MW <1000 can cross the placental barrier.
- All drugs should be considered harmful until proven otherwise.

Mechanism of teratogenicity according to pregnancy stage:

- **Before implantation: (0-17 day):** The effect is all-or-none i.e. either death of the embryo (abortion) or no effect.

- **Early pregnancy: (3-10 weeks):**
  - It is the most dangerous period because it is period of organogenesis.
  - Selective interference can produce characteristic anatomical abnormality e.g. aminoglycosides cause damage to 8th cranial nerve.

- **Late pregnancy:**
  - Gross anatomical abnormalities are less liable to occur.
  - Functional defects rather than anatomical abnormalities can occur especially in organs having delayed formation e.g. brain, testes, and bone.

Examples of teratogenic drugs:

- **ACE inhibitors** and angiotensin receptor blockers cause fetal pulmonary and renal dysfunction.
- **Antithyroid drugs** can cause fetal goiter and hypothyroidism.
- **Tetracycline** antibiotics inhibit growth of fetal bones and stain teeth.
- **Aminoglycosides** cause fetal 8th cranial nerve damage.
- **Warfarin** can cause fetal intracerebral bleeding.
- **NSAIDs** cause premature closure of ductus arteriosus.
- **Benzodiazepines** cause cleft lip and palate.
- **Sex hormones** can cause inappropriate virilization or feminization.
- **Antiepileptic drugs** cause neural tube defect (spina bifida).
- **Cytotoxic drugs** can cause multiple structural damage.

The FDA pregnancy categories:

Category	Definition	Animal	Human
A	Adequate studies in animal and human did not show a risk to the fetus either in the first or in the late trimesters.	✓	✓
B	Animal studies did not show risk to the fetus but there are no adequate studies in human. **or:** Animal studies showed a fetal risk, but adequate studies in human did not show a risk to the fetus.	✓ ×	? ✓
C	Animal studies showed a risk to the fetus but there are no adequate studies in humans; the benefits from the use of the drug in pregnant women may by acceptable despite its potential risks.	×	? **Benefit > Risk**
D	There is evidence of human fetal risk, but the potential benefit of the drug may outweigh its potential risk.	×	× **Benefit > Risk**
X	Studies in animals and humans showed evidence of fetal risk. The potential risk of use in pregnant women clearly outweighs any potential benefit.	×	× **Risk > Benefit**

Part 5: Principles of drug-drug interactions

Classification:

- **Pharmacokinetics interactions.**
- **Pharmacodynamic interactions.**

PHARMACOKINETIC INTERACTIONS

Drug interactions *in vitro*:

e.g. antipseudomonal penicillins and aminoglycosides form complexes in the infusion fluid (see chemotherapy).

Drug interactions *in vivo*:

Absorption

- **Formation of complexes:**
  - Tetracycline forms complexes with Ca^{2+}, Mg^{2+} and Al^{3+}
  - Cholestyramine forms complexes with digitalis and thyroxin.
- **Absorption can be blocked:**
  - Adrenaline ↓ absorption of local anesthetics due to VC.
  - Colchicine ↓ absorption of vitamin B12
- **Change in intestinal motility:**
  - Anticholinergic drugs ⇓intestinal motility → ↑ absorption of some drugs.
  - Prokinetic drugs ↑ intestinal motility → ↓ absorption of some drugs.
- **Changes in gastric pH:**
  - Antacids ↓absorption of salicylates.
  - Ketoconazole is poorly absorbed in absence of gastric acidity.

Distribution

- Sulfonamides displace bilirubin from pl pr in premature infants → kernicterus.
- Phenylbutazone displaces warfarin → excessive bleeding.

Metabolism

- **Inhibition or induction of microsomal metabolism** (see before).
- **Inhibition of non-microsomal enzymes:**
  - MAO inhibitors ↓ metabolism of some drugs e.g. benzodiazepines, serotonin and norepinephrine.
  - Disulfiram inhibits *acetaldehyde dehydrogenase* enzyme → ↓ metabolism of acetaldehyde → accumulation of acetaldehyde causes flushing, nausea, vomiting, and tachycardia.

Excretion

- **Reduction in urinary elimination:**
  - Probenecid ↓ renal excretion of penicillin.
  - Quinidine ↓ renal excretion of digoxin.
- **Changes in urinary pH:**
  - Alkalinization of urine (e.g. sodium bicarbonate) ↑ excretion of weak acids
  - Acidification of urine (e.g. ammonium chloride) ↑ excretion of weak bases.

- **Changes in urinary volume:**
  Diuretics can increase toxicity of some drugs by reducing plasma volume e.g. thiazide can increase lithium toxicity.

- **Stimulation of biliary excretion:**
  Phenobarbital ↑ biliary excretion of many drugs by increasing both bile flow and the synthesis of conjugating proteins.

PHARMACODYNAMIC INTERACTIONS

- **Antagonism:** competitive, non-competitive, chemical, physical, etc.
- **Synergism:** e.g. MAO inhibitors can cause toxic synergism with TCA.
- **Potentiation:** e.g. ethanol can enhance CNS depression caused by opioids
- **Changes in the intracellular or extracellular environment:** e.g. diuretic-induced hypokalemia can ↑ digitalis toxicity.

Notes

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Review Questions

Define the following pharmacokinetic parameters:

- Volume of distribution
- pKa of drugs
- Elimination half life
- First-pass metabolism
- Bioavailability

Mention the clinical significance of each of the following:

- Volume of distribution
- pKa of drugs
- Plasma protein binding of drugs
- Elimination half-life
- Zero-order elimination
- Microsomal enzyme induction
- Hepatic conjugation of drugs

Mention the main differences between:

- Reversible and irreversible antagonism.
- Graded response and quantal response.
- First order elimination and zero order elimination.
- Potency and efficacy.
- Physical and physiological antagonism.
- Habituation and addiction.
- Oxidation and conjugation of drugs.

Discuss 2 pharmacogenetic conditions associated with toxic drug response

Discuss 2 pharmacogenetic conditions associated with reduced drug response

Write short account on antagonism between drugs

Of each of the following questions, select ONE BEST answer:

1. A drug may act by all the following mechanisms EXCEPT:

A. Interaction with protein macromolecules embedded in the cell membranes
B. Interaction with cell membrane ion channels
C. Interaction with intracellular enzymes
D. Interaction with cell membrane phospholipids
E. Interaction with gene functions

2. Ion-channel-linked receptors (direct ligand-gated ion channels) are characterized by:

A. They are the type of receptors principally present in autonomic ganglia and skeletal ms motor end plate
B. They are the type of receptors principally present in vascular endothelium
C. They are rosette-shaped structures consist of 7 membrane subunits
D. Their response is slower than other receptors
E. Activation of these receptors leads to activation of a second messenger

3. Which of the following is classified as belonging to the tyrosine kinase family of receptors:

A. GABA receptors
B. β-Adrenergic receptors
C. Insulin receptors
D. Nicotinic acetylcholine receptors
E. Hydrocortisone receptors

4. All the following are true for intracellular (DNA-linked) receptors EXCEPT:

A. They regulate transcription of genes inside the nucleus
B. Their response is very fast but persists for long time
C. Their agonists must enter inside the cell to reach them inside the nucleus
D. Sex hormones act on these types of receptors
E. Corticosteroids act on these types of receptors

5. The following statements are true for graded dose-response relationship EXCEPT:

A. It is the response to most drugs
B. The response is directly proportional to drug concentration (linear relation)
C. It could be tested in one animal
D. It can be used for comparing the potencies and efficacies of drugs
E. It can be used for calculation of the LD_{50} of drugs

6. The following statements are true for quantal dose-response relationship EXCEPT:

A. It is the response to anticonvulsant and antiarrhythmic drugs
B. The response to the drug is not directly proportional to drug concentration (all-or-none)
C. It could be tested in one animal
D. It helps in calculation of the ED50 and LD50 of drugs
E. It helps in estimation of the degree of drug safety

7. When a drug has a steep dose-response curve, this means:

A. The drug is lethal
B. The drug is expensive
C. The drug is efficacious
D. The drug is safe
E. Minimal change in the dose can lead to dramatic effect.

8. The following statements are true for drug's therapeutic index EXCEPT:

A. It is the relation between the lethal dose in 50% of animals to the curative dose in 50% of them
B. The lower the TI, the safer will be the drug.
C. It should be done to any drug before it's being approved for human use

D. For theoretically useful drugs, it must be greater than 1
E. It could be applied in animal testing

9. The following is true for competitive antagonism:
A. It never occurs with enzymes
B. Is the same as physiological antagonism
C. The agonist can never abolish the effect of the antagonist
D. Is best exemplified by the use of neostigmine to treat curare toxicity
E. Best described as non-surmountable process

10. A drug is said to be reversible antagonist when:
A. It blocks the receptors by making covalent bonds with them
B. The duration of blockade is too long
C. Increasing the dose of the agonist will reverse the block
D. The response curve of the agonist in presence of this drug is not parallel to that of the agonist alone
E. Termination of the drug effect depends on synthesis of new receptors

11. The interaction that may occur between acidic and basic drugs is called:
A. Chemical antagonism
B. Physical antagonism
C. Physiological antagonism
D. Biological antagonism
E. Receptor antagonism

12. The following is true for interactions between drugs:
A. Is not harmful if occurred between drugs having steep dose-response curves
B. Is not harmful if occurred between drugs having narrow therapeutic ratios
C. Is not harmful if occurred between drugs undergoing zero-order kinetics
D. May lead to valuable therapeutic effects
E. Is described as addition if the action of one drug abolishes the effects of another

13. A drug may interact with ion channels by all of the following mechanisms EXCEPT:
A. The drug may change the ion channel structure
B. The drug may block the channel physically
C. The drug may change an intracellular ATP on which the channel depends
D. The ion channel may be part of ion channel-linked receptors
E. The ion channel may be modulated by G-protein linked receptors

14. Failure of the patient to breath after surgical operation may be due to:
A. Pseudocholinestrase deficiency
B. Methemoglobin reductase deficiency
C. G-6-PD deficiency
D. Vitamin K epoxide reductase deficiency
E. Monoamine oxidase deficiency

15. Hemolysis that may occur with sulfonamides therapy may be due to:
A. Pseudocholinestrase deficiency
B. Methemoglobin reductase deficiency
C. G-6-PD deficiency
D. Vitamin K epoxide reductase deficiency
E. Monoamine oxidase deficiency

16. Severe myelosuppression following 6-mercaptopurine therapy is most likely due to:
A. Pseudocholinestrase deficiency
B. Methemoglobin reductase deficiency
C. G-6-PD deficiency
D. Vitamin K epoxide reductase deficiency
E. Thiopurine methyltransferase deficiency

17. Hepatic toxicity that may accompany isoniazide therapy may be due to:

A. Defective oxidation reaction
B. Defective conjugation reaction
C. Defective deamination reaction
D. Slow acetylation reaction
E. Rapid acetylation reaction

18. Failure of some children with rickets to respond to therapeutic doses of vitamin D is most likely to be due to:
A. Differences in sex
B. Differences in body weight
C. Genetic variation
D. Tolerance
E. Intolerance

19. The following are true for overshot phenomenon (drug intolerance) EXCEPT:
A. It occurs due to down-regulation of receptors
B. It occurs after sudden stoppage of some drugs given for long time
C. It may lead to serious withdrawal effects
D. It can be avoided by gradual cessation of drugs
E. It is best exemplified by occurrence of severe tachycardia after sudden stopping of beta blockers.

20. The following statements are true for pKa of drugs EXCEPT:
A. Ionized drugs are poorly absorbed while unionized drugs are more absorbed
B. Ionization of most drugs depends on the pH of the medium around them
C. pKa of drugs can help knowing the site of drug absorption.
D. Acidic drugs become more absorbable in alkaline pH
E. Basic drugs become more reabsorbable in alkaline urine

21. Which of the following drugs will be absorbed to the LEAST extent in the stomach:
A. Ampicillin (pKa = 2.5)
B. Aspirin (pKa = 3.5)
C. Warfarin (pKa = 5.0)
D. Phenobarbital (pKa = 7.4)
E. Propranolol (pKa = 9.4)

22. The following statements are true for Vd of drugs EXCEPT:
A. It can exceed the volume of water in the body
B. Drugs with large Vd can be removed by dialysis
C. Would be expected to be 5L if the drug is confined to the blood.
D. Highly lipid-soluble drugs would be expected to have large Vd
E. It can help in the calculation of the total amount of the drug in the body

23. The plasma half-life ($t_{1/2}$) of drugs:
A. Is expressed as the percentage that remains ½ hour after administration
B. Will be short if the drug gets into the enterohepatic circulation
C. Cannot be calculated if the drug is excreted through the bile
D. Is constant for drugs having zero-order elimination
E. Can be prolonged by slowing the rate of drug elimination

24. The bioavailability of a drug:
A. Is defined as the actual blood concentration required to produce a pharmacological effect
B. Will be unaffected by changes in formulation
C. May be affected by liver damage
D. Must be 100% for a drug given by mouth and is completely absorbed
E. Is a term applied only to oral administration

25. All the following are phase I biotransformation reactions EXCEPT:
A. Sulfate conjugation
B. Xanthine oxidation
C. Nitroreduction
D. Ester hydrolysis
E. Oxidative deamination

26. Metabolism (biotransformation) of drugs can lead to all the following results EXCEPT:

A. Conversion of active compound into inactive metabolites
B. Conversion of active compound into active metabolites
C. Conversion of inactive compound into active metabolites
D. Conversion of non-toxic compound into toxic metabolites
E. Conversion of water-soluble compound into lipid-soluble metabolites

27. All the following statements are true for First-order kinetics EXCEPT:

A. Apply to most drugs in clinical use
B. Apply to salicylate (aspirin) metabolism within small dose.
C. The concentration versus time curve is non-linear.
D. The rate of elimination depends on plasma concentration of the drug
E. Steady state plasma concentration can be reached after 5 half lives

28. All the following statements are true for zero-order kinetics EXCEPT:

A. Elimination rate is independent of the dose
B. Elimination depends on saturable enzyme system
C. Plasma concentration of the drug cannot be expected at any time
D. The t1/2 of the drug is not constant
E. There is no fear from drug cumulation or interactions

29. Drugs X and Y have the same mechanism of diuretic action. Drug X in a dose of 5mg produces the same magnitude of diuresis as 500 mg of drug Y. This suggests that:

A. Drug Y is less efficacious than drug X
B. Drug X is about 100 times more potent than drug Y.
C. Toxicity of drug X is less than that of drug Y.
D. Drug X is a safer drug than drug Y.
E. Drug X will have a shorter duration of action than drug Y because less of drug X is present for a given effect.

30. Which of the following terms best describes the antagonism of leukotriene's bronchoconstrictor effect (mediated at leukotriene receptors) by terbutaline (acting at adrenoceptors) in a patient with asthma?

A. Pharmacologic antagonist.
B. Partial agonist.
C. Physiologic antagonist.
D. Chemical antagonist.
E. Noncompetitive antagonist.

31. Which of the following provides information about the variation in sensitivity to the drug within the population studied?

A. Maximal efficacy.
B. Therapeutic index.
C. Drug potency.
D. Graded dose-response curve.
E. Quantal dose-response curve.

32. Which of the following provides information about the largest response a drug can produce, regardless of dose?

A. Drug potency.
B. Maximal efficacy.
C. Mechanism of receptor action.
D. Therapeutic index.
E. Therapeutic window.

33. A pro-drug is:

A. The prototype member of a class of drugs.
B. The oldest member of a class of drugs
C. An inactive drug that is transformed in the body to an active metabolite.
D. A drug that is stored in the body tissues and is then gradually released in the circulation.
E. Ionized drug trapped in breast milk.

34. If the rate of infusion of a drug were doubled, what response in the steady

state concentration would be expected?

A. Remain unchanged
B. Doubled
C. Increase 50%
D. Decrease 50%
E. Decrease 100%

35. Half-life of a drug may be helpful to determine:

A. Elimination of the drug
B. Level of absorption
C. Rate of absorption through the GIT
D. Time to reach the steady state
E. Distribution into body systems.

36. What determines the degree of movement of a drug between body compartments?

A. Partition constant
B. Degree of ionization
C. pH
D. Molecular size
E. All of the above

37. For intravenous (IV) dosages, what is the bioavailability assumed to be?

A. 0%
B. 25%
C. 50%
D. 75%
E. 100%

38. Which of the following can produce a therapeutic response? A drug that is:

A. Bound to plasma albumin
B. Concentrated in the bile
C. Concentrated in the urine
D. Not absorbed from the GI tract
E. Unbound to plasma proteins

39. Aspirin is a weak organic acid with a pKa of 3.5. What percentage of a given dose will be in the lipid-soluble form at a stomach pH of 1.5?

A. About 1%
B. About 10%
C. About 50%
D. About 90%
E. About 99%

40. Concerning the renal excretion of drugs:

A. Drugs that are ionized in the renal tubules are more likely to undergo passive reabsorption.
B. Low MW drugs are much more likely to be actively secreted than filtered.
C. Only the fraction of the drug that is unbound (free) to plasma proteins is filtered by the glomerulus.
D. Decreasing urinary pH enhance excretion of weakly acidic drugs.
E. Renal clearance cannot exceed the GFR (125 ml/min).

41. In which of the following cases could a graded dose-response curve be constructed?

A. Prevention of convulsions
B. Prevention of arrhythmias
C. Reduction of death
D. Reduction of fever
E. Relief of insomnia

42. Which of the following can be used as a relative indicator of the margin of safety of a drug?

A. T.I.
B. LD50
C. ED50
D. EC50
E. TD50

43. Flurazepam has a pKa of 8.2. What percentage of flurazepam will be ionized at a urine pH of 5.2?

A. 0.1%
B. 1.0%
C. 50%
D. 99%
E. 99.9%

44. Which route of administration is most likely to subject a drug to first pass metabolism?

A. Intravenous
B. Sublingual
C. Oral

D. Inhalation
E. Intramuscular

45. If a drug was given by a constant infusion rate, which of the following factors determines how long it will take for the drug to reach a steady-state concentration (Cpss) in the blood?
A. Apparent volume of distribution
B. Bioavailability
C. Clearance
D. Half-life
E. Infusion rate (mg of drug/min)

46. Which of the following best describes what the term "tachyphylaxis" means?
A. An increase in the rate of the response, for example, an increase of the rate of muscle contraction
B. Immediate hypersensitivity reactions (i.e., anaphylaxis)
C. Prompt conformational changes of the receptor such that agonists, but not antagonists, are able to bind and cause a response
D. Quick and progressive rises in the intensity of drug response, with repeated administration, even when the doses are unchanged
E. Rapid development of tolerance to the drug's effects

47. Drug A undergoes a series of Phase I metabolic reactions before being eliminated. Which of the following statements best describes the characteristics of Drug A, or the role of Phase I reactions in its metabolism?
A. Complete metabolism of Drug A by Phase I will yield products that are less likely to undergo renal tubular reabsorption
B. Drug A is a very polar substance
C. Drug A will be biologically inactive until it is metabolized
D. Phase I metabolism of Drug A involves conjugation with glucuronic acid or sulfate
E. Phase I metabolism of Drug A will increase its intracellular access and actions

48. The FDA assigns the letters A, B, C, D, and X to drugs approved for human use. To which of the following does this classification apply?
A. Amount of dosage reduction needed as serum creatinine clearances fall
B. Fetal risk when given to pregnant women
C. Amount of dosage reduction needed in presence of liver dysfunction
D. Relative margins of safety/therapeutic index
E. The number of unlabeled uses for a drug

49. Which effect may lead to toxic reactions when a drug is taken continuously or repeatedly?
A. Refractoriness
B. Cumulative effect
C. Tolerance
D. Tachyphylaxis
E. Intolerance

50. Tolerance and drug resistance can be a consequence of:
A. Change in receptors, loss of them or exhaustion of mediators
B. Increased receptor sensitivity
C. Decreased metabolic degradation
D. Decreased renal tubular secretion
E. Activation of a drug after hepatic first-pass

51. If two drugs with the same effect, taken together, produce an effect that is equal in magnitude to the sum of the effects of the drugs given individually, it is called as:
A. Antagonism
B. Potentiation
C. Synergism
D. Additive effect
E. Supersensitivity

52. All of the following statements about efficacy and potency are true EXCEPT:

A. Efficacy is usually a more important clinical consideration than potency

B. Efficacy is the maximum effect of a drug

C. Potent drugs usually given in small dose.

D. Potency is a comparative measure, refers to the different doses of two drugs that are needed to produce the same effect

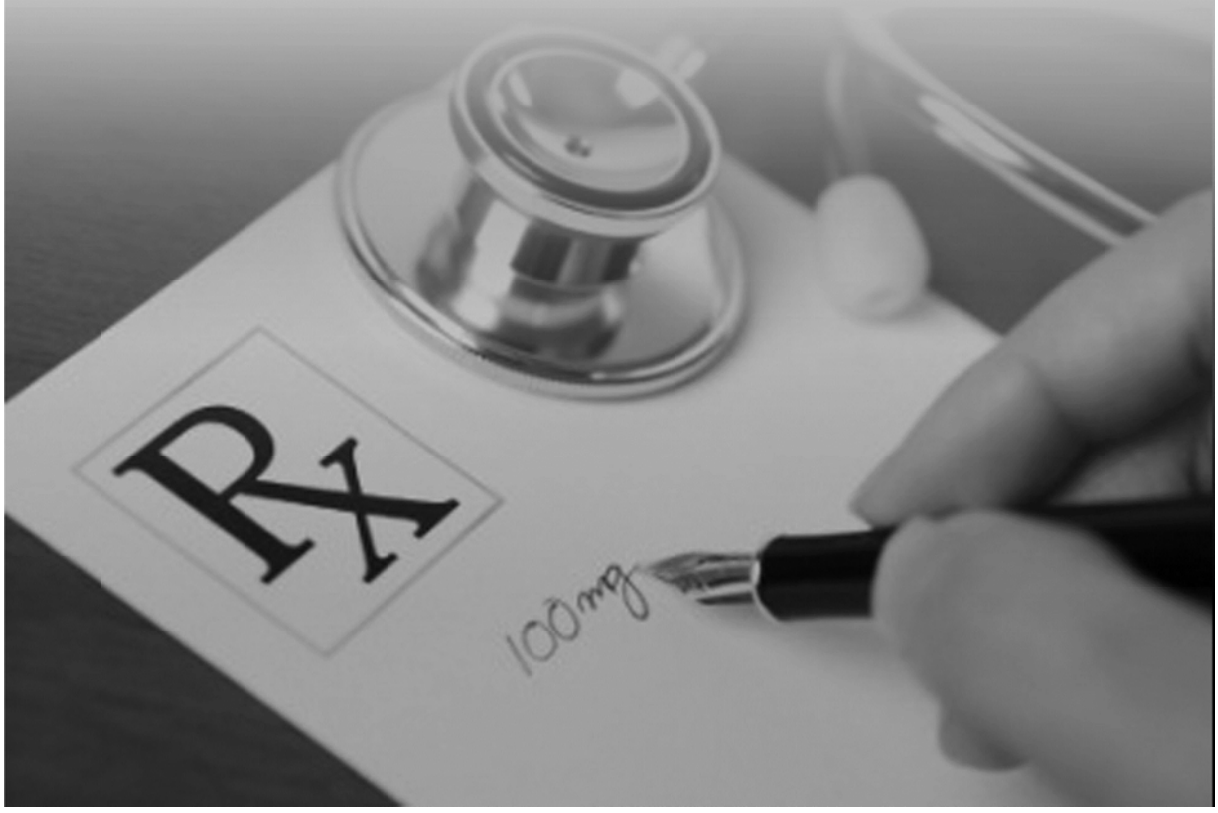
E. The ED50 is a measure of drug's efficacy

Answers

1 D	11 A	21 E	31 E	41 D
2 A	12 D	22 B	32 B	42 A
3 C	13 A	23 E	33 C	43 E
4 B	14 A	24 C	34 B	44 C
5 E	15 C	25 A	35 D	45 D
6 C	16 E	26 E	36 E	46 E
7 E	17 E	27 C	37 E	47 A
8 B	18 C	28 E	38 E	48 B
9 D	19 A	29 B	39 E	49 B
10 C	20 D	30 C	40 C	50 A
				51 D
				52 E

Chapter 2

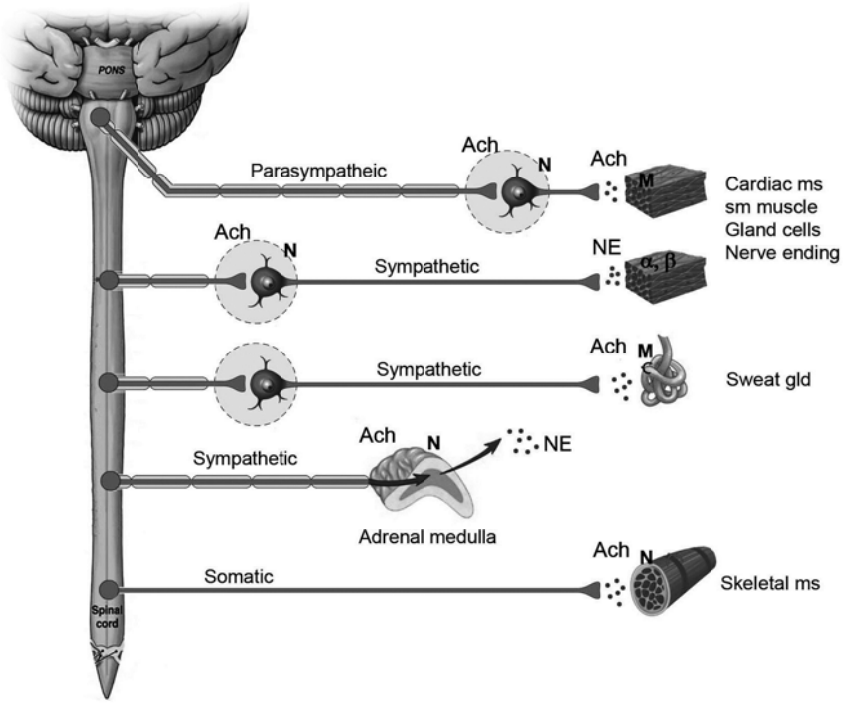
Autonomic Pharmacology



Chapter 2
Autonomic Pharmacology

Part 1: Basic information

The autonomic nervous system controls **involuntary activity** (Fig 1, table 1).



Sympathetic nervous system (SNS)

- Short preganglionic axons originate from thoracic and lumbar areas of the spinal cord and synapse in ganglia located close to the spinal cord.
- The adrenal medulla is considered a *modified ganglion* and is innervated by sympathetic fibers.
- Thermoregulatory **sweat glands** are anatomically sympathetic, but the postganglionic nerve fibers release acetylcholine (ACh) *(i.e. sympathetic cholinergic)*.

Parasympathetic nervous system (PNS)

- Long preganglionic axons originate from cranial and sacral areas of the spinal cord and synapse in ganglia located **close to** or **within** the innervated organ (with few exceptions).
- Short postganglionic axons innervate many tissues and organs as the SNS.
- Parasympathetic innervation predominates over sympathetic innervation of most organs **except blood vessels** *(have only sympathetic supply)*.

Enteric nervous system (ENS)

- The ENS is considered the third division of the ANS.
- It is a collection of neurons inside the wall of the GIT that controls the motility, exocrine and endocrine secretions of the GI tract.
- Nerve terminals contain peptides and purines as neurotransmitters.
- This system functions independently of the CNS and is modulated by both SNS and PNS.

The somatic nervous system controls voluntary activity**:**

- Long axons originate in the spinal cord and directly innervate **skeletal muscles** (no ganglia).
- Nerve terminals in the **neuromuscular junction** release **Ach** as the neurotransmitter.

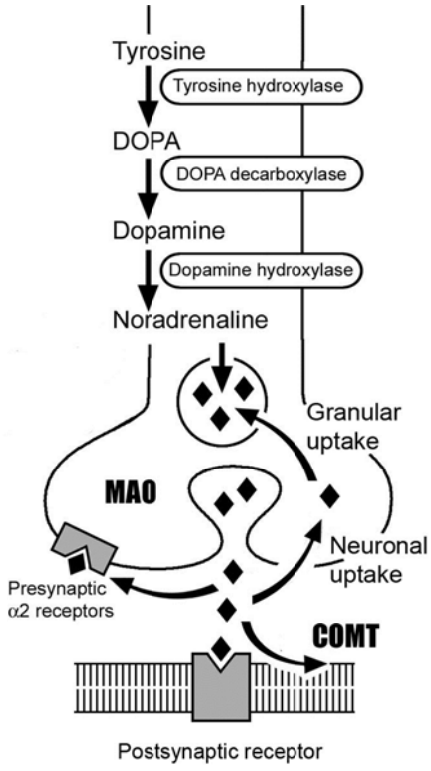
Neurotransmitters of the ANS

1. Norepinephrine and epinephrine

They are **catecholamines,** having catechol nucleus.

Biosynthesis of catecholamines:

- In nerve endings, tyrosine is hydroxylated by *tyrosine hydroxylase* to form (dopa); dopa is then decarboxylated to form dopamine which is hydroxylated into norepinephrine inside storage vesicles.
- In certain areas of the brain and in the adrenal medulla, norepinephrine is methylated by *N-methyltransferase* to form epinephrine.



Storage and release:

- Norepinephrine is stored in vesicles in nerve terminals.
- Norepinephrine also exists in a non-vesicular cytoplasmic pool that is released by indirectly acting sympathomimetics (e.g., **tyramine, amphetamine**).

Termination:

- **Re-uptake (80%):** mainly in the form of:
  - Neuronal uptake (into neuronal cytoplasm).
  - Granular uptake (into storage vesicles).
- **Metabolism (18-20%):**

- **Monoamine oxidase (MAO) enzyme:** metabolizes norepinephrine in neuronal cytoplasm.
  - MAO-A: present in the brain and peripheral tissues (e.g. liver & intestine).
  - MAO-B: present mainly in the **B**rain and more active on **dopamine**. It has little effect on norepinephrine and serotonin.
- **Catechol-O-methyl transferase (COMT):** metabolizes norepinephrine in synaptic space.

N.B. The end-product of catecholamine metabolism is *vanillyl mandelic acid (VMA)*. The normal urinary level of VMA is 4-8 mg/day. Higher levels indicate tumor in suprarenal medulla **(pheochromocytoma,** Fig 3).

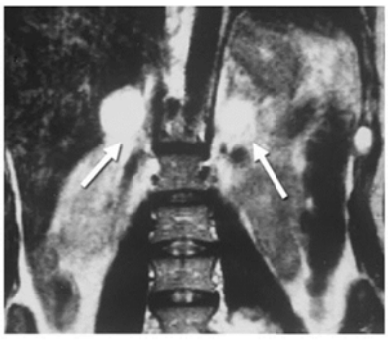


Figure 3. MRI abdomen showing bilateral suprarenal masses typical with pheochromocytoma

Clinical correlates:

Depression is associated with decreased activity of NA and/or serotonin at the level of synapse. Tricyclic antidepressant drugs act by inhibition of neuronal uptake of NA and serotonin while MAO inhibiting drugs act by inhibition of their metabolism. Both mechanisms lead to accumulation of NA and serotonin at the synaptic levels.

Parkinsonism is associated with deficiency of dopamine in the negrostriatal pathway. Inhibition of MAO-B enzyme (selegiline) and COMT enzyme (tolcapone) leads to accumulation of dopamine and improvement of bradykinesia.

2. Acetylcholine (ACh)

- ACh is synthesized in nerve terminals from acetyl co-A and choline. Synthesized ACh is stored in vesicles in nerve terminal.
- **Botulinum toxin** blocks Ach release and causes skeletal muscle paralysis.
- The main fate of ACh is rapid hydrolysis by **cholinesterase** (ChE) enzyme; there are **two isoforms**:

True ChE	Pseudo ChE
– Present in CNS, ganglia, NMJ.	– Present in plasma and liver.
– Specific for Ach.	– Not specific for Ach
– Deficiency is fatal.	– Deficiency is Not fatal
– Regenerates in 2-3 months.	– Regenerates in 2-3 weeks.

Clinical correlates:

Congenital PsChE deficiency (succinylcholine apnea):

Succinylcholine is a neuromuscular blocker that is metabolized by PsChE enzyme. Some individuals have congenital deficiency of PsChE, when they take succinylcholine to produce muscle relaxation before surgery, severe muscle paralysis occurs due to lack of succinylcholine metabolism. Death may occur from paralysis of respiratory muscles. Urgent blood transfusion and artificial respiration may be required.

3. Co-transmitters

A number of **Non-adrenergic-Non-cholinergic** (NANC) transmitters may be found in association with NA or Ach in the autonomic nerve terminals. **T**hey are released with the primary transmitter to play a **regulatory function**. Examples include: *neuropeptide Y; encephalin; histamine; 5HT; ATP; PGs; and nitric oxide (NO)*.

Table 1. Distribution and functions of **autonomic receptors.**

Tissue	SYMPATHETIC		PARASYMPATHETIC	
	R	**Effect**	**R**	**Effect**
Heart	β_1	↑ all cardiac properties (tachycardia, ↑A-V conduction, ↑contractility, etc)	M_2	↓ SA node activity and AV conduction (NOT **atrial conduction)**
Blood vessels	α_1 β_2	VC of most BV VD of skeletal muscle BVs, and coronary artery.	M_3*	VD of most BV (through release of EDRF). ***N.B.*** *Most vascular M3 receptors are non-innervated*
Bronchi				
Smooth ms Glands	β_2 α_1	Relaxation (Bronchodilatation) ↓ Bronchial secretion	M_3 M_3	Contraction (Bronchoconstriction) ↑ Bronchial secretion
GIT				
Wall	α, β_2	Relaxation (↓ motility)	M_3	Contraction (↑ motility)
Sphincters	α_1	Contraction	M_3	Relaxation
Salivary gld	α_1	↑ enzyme secretion (viscid saliva)	M_3	↑ water secretion (salivation)
Liver	β_2	Glycogenolysis		–
Stomach HCl		–	M_1	↑ HCl secretion
U bladder				
Detrusor ms	β_2	Relaxation	M_3	Contraction
Sphincter	α_1	Contraction (urine retention)	M_3	Relaxation (urine flow)
Uterus	β_2 α_1	Relaxation Contraction		–
♂ **organs**	α_1	Ejaculation	M_3	Erection
Kidney	β_1	↑ Renin secretion		–
Skeletal ms	β_2	Tremors and enhancement of neuromuscular transmission		–
Eye				
Iris ms	α_1	Pupil dilatation (mydriasis)	M_3	Pupil constriction (miosis)
Ciliary ms	β_2	Relaxation (distant vision)	M_3	Contraction (near vision)
IOP	β_2	↑ aq humor secretion (↑ IOP)	M_3	↑ aq humor **drainage** (↓ IOP)
Lacrimal gld		–	M_3	↑ lacrimal secretion
Sweat gld	α_1	↑ sympathetic sweating (forehead & palms)	M_3	↑ Thermoregulatory sweating (cholinergic sweating)
Fat cells	**β_3**	**Lipolysis**		–
Mast cells	β_2*	↓ histamine release		–
Plasma K^+	β_2	Decrease plasma K^+		–
Nerve terminals	α_2 β_2	↓ NA release ↑ NA release		–

* = **Non-innervated receptors** i.e. receptors are found in the organ but have **no** autonomic nerve supply. They can respond only to circulating or administered agonists.
EDFR = endothelial derived relaxing factor = nitric oxide (NO).

Table 2. Summary of adrenergic receptors

	α_1	α_2	β_1	β_2	β_3
2nd msngr	G_q (↑ IP3 & ↑ DAG) →↑ Ca^{2+}	G_i (↓ cAMP)	G_s (↑ cAMP)	G_s (↑ cAMP)	G_s (↑cAMP)
Sites and function	1. VC of **most** bl vessels (α_{1A}) 2. Contraction of all sphincters (GIT, urinary). 3. Contraction of dilator pupillae ms (mydriasis) 4. Contraction of uterus 5. Relaxation of GIT & UB walls 6. Adrenergic sweating (forehead & palm)	1. **Presynaptic** nerve endings **(↓ NA release)** 2. **Central:** ↓ central sympathetic outflow 3. Relaxation of GIT & UB walls	1. ↑ all cardiac properties 2. ↑ renin release (kidney)	1. **Presynaptic** nerve endings **(↑ NA release**) 2. **Central:** ↑ central sympathetic outflow 3. VD of sk ms bl vessels and coronary artery 4. Bronchodilatation 5. Relaxation of GIT & UB walls 6. Relaxation of uterus 7. Skeletal muscle tremors 8. ↑ aqueous humor secretion 9. ↑ liver glycogenolysis 10. ↓ plasma K^+	↑ lipolysis (adipose tissue)
Sel. agonist	Phenylepherine	Clonidine	Dobutamine	Salbutamol	
Selective antagonist	Prazosin	Yohimbine	Atenolol	Butoxamine *(not used clinically)*	
Non-selec agonist	Adrenaline Ephedrine				
Non-selec antagonist	Phenoxybenzamine Ergot alkaloids		Propranolol Timolol		

- β_4 and β_5 are also present but still under investigation.
- In most smooth muscles, the α1 receptors mediate contraction through activation of Ca^{2+} dependent *myosin light chain kinase* but in the GIT smooth muscles, they mediate relaxation through hyperpolarization caused by opening of Ca^{2+} dependent K^+ channels.
- **α1** receptors have 3 subtypes, A, B, and D; **α2** receptors have three subtypes: A, B, and C.

Table 3. Summary of cholinergic receptors

	M_1	M_2	M_3	N_n	N_m
2nd msngr	**G_q** (↑ IP3 & ↑ DAG) →↑ **Ca^{2+}**	**G_i** (↓cAMP)	**G_q** (↑ IP3 & ↑ DAG) →↑ **Ca^{2+}**	**Ion channel**	**Ion channel**
Sites and function	1. **CNS** 2. **Stomach** → ↑ HCL secretion	↓↓ SAN activity and AV conduction *(not atrial conduction)*	1. **VD** of most **BV** through synthesis of *endothelial-derived relaxing factor* (EDRF) → ↓ **blood pressure.** 2. **Contraction** of all wall smooth muscles (bronchi, GIT, UB) and **relaxation** of all sphincters. 3. ↑↑ **all body secretions** (sweating, salivation, lacrimation, etc). 4. **Eye:** → miosis & ciliary muscle contraction (accommodation for near vision).	**All autonomic ganglia** and adrenal medulla	**NMJ** → skeletal muscle contraction
Selective antagonist	Pyrenzepine	Gallamine	---------	Trimetaphan	d-tubocurarine
Non-selec agonist	Acetylcholine				
Non-selec antagonist	Atropine - hyoscine				

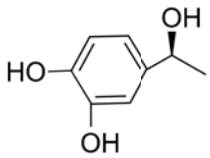
N.B.

- **M4** and **M5** are also present in the **CNS.**
- **M1 – M3 – M5** are linked to Gq (↑ IP3 & ↑ DAG).
- **M2 – M4** are linked to Gi (↓ cAMP)

Part 2: Adrenergic agonists (Sympathomimetics)

Actions and chemical structure

- These drugs act either **directly** or **indirectly** (by release of norepinephrine stored), to activate adrenergic receptors and mimic the effects of endogenous catecholamines.
- Not all sympathomimetic drugs activate the adrenergic receptors by the same degree; some drugs have higher affinity towards certain receptor class (**selectivity)** depending on the **ultrastructure** of these receptors; however, in **large doses, this selectivity is lost**.
- Chemically, these drugs may contain catechol nucleus, **(i.e. catecholamines)** or not **(non-catecholamines)**.
- Catecholamines *(e.g. epinephrine, norepinephrine, isoproterenol,* and *dopamine)* are **characterized by:**
  - They are **not absorbed** orally and **cannot pass** the BBB.
  - They have very **short duration** due to **rapid inactivation** by MAO and COMT.



atechol

DIRECT- ACTING SYMPATHOMIMETIC DRUGS

1. Epinephrine (Adrenaline)

Chemistry and pharmacokinetics

- Epinephrine is a natural catecholamine neurotransmitter. Synthetic epinephrine is **poorly absorbed** from the GI tract and **does not pass BBB** to any extent.
- It is administered **parenterally** (i.m. and s.c.). The s.c. absorption is slow due to local VC.
- Nebulized forms (inhalation) are also available.
- It is metabolized rapidly by COMT and MAO. Metabolites are excreted in urine.

Mechanism and pharmacological effects

- Epinephrine activates **all α and β-**adrenoceptors.
- **β** receptors mediate their effects through increase intracellular cAMP.
- **α1** receptors mediate their effects through increase intracellular **I**P3 and DAG.

CVS (The major action)

- Increase **rate** (chronotropic effect) and **force** (inotropic effect) of the cardiac muscle (β1); it may precipitate angina in patients with coronary insufficiency.
- **Increases systolic pressure** due to positive inotropic and

chronotropic effects (β1), and **decreases diastolic pressure** (because VD of skeletal muscle blood vessels (β2) overcomes the VC produced by α1 receptors in skin and splanchnic vascular beds).

- At high doses, VC (α1) of **all vascular beds** predominates leading to **increase both** systolic and diastolic BP.
- Increase coronary blood flow due to increased cardiac work (accumulation of metabolites), and β2 stimulation (VD).

Respiratory system
- Relaxation of bronchial smooth muscle (β2).
- Decrease bronchial secretions (α1).

Eye
- Mydriasis due to contraction of dilator pupillae muscle (α1)

Metabolic effects
- Hyperglycemia due to stimulation of hepatic glycogenolysis (β2).
- Lipolysis and increase free fatty acids in blood.

Therapeutic uses (emergency conditions)

- **Anaphylactic shock:**
  - It is a life-threatening condition (acute hypersensitivity reaction) resulting from massive release of histamine from inflammatory cells in response to exposure to allergic substance (e.g. penicillin). Histamine causes severe hypotension and bronchoconstriction by its effect on histamine (H1) receptors.
  - Injection of epinephrine immediately dilates the bronchi (β2), decreases bronchial secretions (α1), and elevates BP (VC); so, epinephrine is considered the "**physiological antidote"** of histamine as it can reverse all its effects by actions on different receptors.
  - It is given 0.5 ml (1:1000) i.m. (ideally in the lateral thigh muscles) and could be repeated /5 min if no response.

- **Acute bronchospasm:** within minutes after s.c. administration, epinephrine induces bronchodilation (β2) and decrease airway edema (α1); however, short-acting selective β2 agonists could be used with fewer CVS side effects.

- **Cardiac arrest:** early i.v. epinephrine administration, during cardiopulmonary resuscitation (CPR), can restore cardiac activity (β1) and improve vascular tone collapse (α1). Recommended dose is 1 ml of 1:1000 i.v. or 10 ml 1:10000 i.v.

- **With local anesthetics:** diluted concentrations of epinephrine (1:10000) or norepinephrine are sometimes added to local anesthetics to produce local VC; this will prolong the duration of the anesthetic (due to ↓ absorption of the anesthetic) and reduce bleeding.

Adverse effects

- Cerebral hemorrhage: due to marked elevation of BP.
- Anginal pain from excessive cardiac work and strain.
- Cardiac arrhythmia: especially if given with digoxin, or if given i.v. (i.v. epinephrine can produce fatal ventricular fibrillation).
- Acute pulmonary edema: due to increase both systemic and pulmonary pressures, this cause acute rise of intrapulmonary hydrostatic pressure with hydrostatic flux of fluid.

Contraindications

- **Presence of hypertension:** as it may cause cerebral hemorrhage.
- **Ischemic heart disease.**
- **Cardiac arrhythmia or with digitalis:** epinephrine can worsen the arrhythmia and even precipitate ventricular fibrillation.
- **Cardiac outflow obstruction** (e.g. severe aortic stenosis, severe pulmonary hypertension, hypertrophic obstructive cardiomyopathy). In these conditions, epinephrine will increase contractility of the cardiac muscle against a narrow outlet, so it can precipitate acute pump failure.
- **Thyrotoxicosis:** because patients with thyrotoxicosis have increased sympathetic overactivity (tachycardia, tremors, anxiety, etc) due to **increased sensitivity** of β receptors.

2. Norepinephrine

- It activates **α (mainly) and β1-receptors** leading to increase both systolic and diastolic BP with **reflex bradycardia**.
- It has little activity on β2-receptors.
- It is used as VC (by slow i.v. infusion) in acute hypotensive states.

3. Dopamine

- It is a natural catecholamine given by i.v. infusion because it has very short duration of action (2 min).
- **In low doses:** stimulates dopamine **D1** receptors in renal and mesenteric vascular beds leading to **VD** and increase renal and hepatic blood flow.

The baroreceptor reflex

- It is a physiological reflex concerned with regulation of BP.
- Sudden increase of BP → activation of stretch receptors in the carotid sinus and aortic arch → afferent impulses through the vagus to the CVS centers in the medulla→ decrease HR and vascular tone. Hypotension has opposite effect.
- These receptors begin to respond at pressures ≥170 mm Hg.
- In chronic hypertension, this set point is shifted to higher level.
- Baroreflex is blocked by **atropine.**

- **In intermediate doses:** stimulates **cardiac β1** receptors leading to increase contractility and COP.
- **In large doses:** stimulates **vascular α1** receptors leading to VC and ↑↑ **BP**.

Therapeutic uses

- **Shock states:**

– Shock is a complex state of hypotension associated with impaired tissue perfusion of the vital organs (brain, liver, kidney, etc.).
– Dopamine, given by continuous i.v. infusion, restores adequate tissue perfusion by increasing COP (β1), and increasing renal blood flow (RBF) and glomerular filtration rate (GFR; D1). In high doses, it also stimulates vascular α1 receptors leading to improvement of vascular tone collapse and elevation of BP.
– **N.B.** If vasopressors (e.g. noradrenaline) are given alone, they will elevate BP but aggravate tissue ischemia due to VC.

4. β-adrenoceptor agonists:

a. Selective β1 agonist: Dobutamine

- Dobutamine is a synthetic catecholamine that is related to dopamine. It is administered by i.v. infusion because of its short duration (2 min).
- It activates mainly **cardiac β1**-receptors with **no effect** on dopamine receptors leading to increase COP with little or no vascular effects.
- It is given by continuous i.v. infusion in **cardiogenic shock** (a complication of left ventricular infarction), to reverse myocardial depression and increase COP (β1).

Dopamine	Dobutamine
– Natural catecholamine – Stimulates D > β1 > α1 – Used for treatment of most cases of shock	– Synthetic catecholamine – Stimulates β1 only – Used mainly for treatment of cardiogenic shock

b. Selective β2 agonists:
Salbutamol, terbutaline, salmetrol, formoterol, ritodrine

- They are synthetic non-catecholamines.
- Salbutamol and terbutaline have **short** duration – salmetrol and formoterol have **long** duration.
- They have greater selectivity at **β2** receptors leading to relaxation of bronchial and uterine smooth muscles, and decrease peripheral resistance (VD).
- **In high doses**, selectivity on β2 receptors is **lost,** leading **tachycardia** and even **arrhythmia** (β1).

Therapeutic uses:

- Treatment of **bronchial asthma** (see respiratory for more details).
- **Ritodrine** is commonly used to induce uterine relaxation and delay preterm labor.

Adverse effects

- High doses can cause hypotension (from VD), tachycardia and **arrhythmia** due to loss of selectivity.
- **Tremors:** β2 receptors in skeletal muscles neuromuscular junction facilitate neuromuscular transmission and induce tremors.

c. Non-selective β agonist: Isoproterenol (Isoprenaline)

- Synthetic catecholamine that predominantly stimulates **both β1& β2** receptors.
- It increases HR and contractility, and relax bronchial smooth muscles.
- It is used as a bronchodilator; however, its **nonselectivity** is one of the major drawbacks that makes it **rarely used therapeutically**.

5. α-adrenoceptor agonists:

a. Phenylephrine, methoxamine, and medodrine

- They are non-catecholamines having long duration of action.
- They selectively stimulate **α1**-receptors leading to VC, and increased both systolic and diastolic pressures with **reflex bradycardia**.
- They are used as vasopressors to correct hypotension.
- They could be used **locally** as eye or **nose drops** to produce VC and relieve congestion (i.e. nasal decongestants).

b. Xylometazoline and oxymetazoline

- These drugs stimulate both **α1 and α2** receptors but with slight selectivity toward **α1** receptors.
- They are primarily used **locally** as eye or **nose drops** to produce VC **(nasal decongestants)**.

Adverse effects and precautions

- Sufficient concentrations may be absorbed systemically and produce severe **hypertension** (even stroke); so they must be avoided in hypertensive patients.
- Prolonged and continuous use (> 3 weeks) may lead to **atrophy** of the nasal mucosa (due to VC); so they should be used for the minimum duration.
- Repeated local application leads to **rebound** severe congestion, so they must be used with the minimal dose and for the shortest duration.

c. Clonidine

- It is a centrally acting **α2** agonist leading to **decrease central sympathetic outflow** and **blood pressure** (see page 55).

d. Tizanidine

- It is another centrally acting **α2** agonist (congener of clonidine) with greater effect on presynaptic α2 in the **spinal cord,** so it inhibits neurotransmission and reduces muscle spasm with minimal effect on blood pressure.
- It is used as **skeletal muscle relaxant** in various spastic conditions such as multiple sclerosis, back pain, and spine injuries.

6. Dopamine receptor agonists: Fenoldopam

- It stimulates peripheral dopamine (**D1)** receptors in renal and mesenteric arteries, leading to VD and decrease peripheral resistance.
- It is used parenterally as a **rapid-acting vasodilator** to treat **emergency hypertension** in hospitalized patients.

INDIRECT- ACTING SYMPATHOMIMETIC DRUGS

1. Amphetamine and its derivatives

- Amphetamine and its derivatives are **indirect-acting** adrenergic drugs. They mediates their primarily action by **blocking neuronal uptake** of dopamine and norepinephrine and **promoting their release** from store sites in the CNS and synapses.
- Amphetamine **stimulates** the entire CNS, cortex, brainstem, and medulla. This leads to increased alertness, decreased fatigue, depressed appetite, and insomnia.

Therapeutic uses

– **Methylphenidate** is an amphetamine derivative used in the treatment of attention-deficit/ hyperactivity disorder (ADHD) of children.
– **Modafenil** is another derivative used for treatment of narcolepsy.

Attention deficit hyperactivity disorder (ADHD)

It is a neuropsychiatric disorder appears after the age 6 years. The child is hyperkinetic and lacks attention in addition to poor school performance.

The amphetamine derivative **methylphenidate** is a CNS stimulant that can improve attention spans allowing better function in school, and reduces hyperkinesia associated with this syndrome.

Adverse effects

– High doses cause anxiety, seizures, hypertension, chest pain, and life-threatening arrhythmia.
– Psychosis, hallucinations, and drug dependence.

Narcolepsy is a chronic neurological disorder characterized by intermittent, uncontrollable episodes of falling asleep during the daytime. These sudden sleep attacks may occur during any type of activity at any time of the day.

2. Cocaine

- Cocaine is an alkaloid derived from the coca plant. It is widely **abused** as a recreational stimulant.
- It **inhibits neuronal uptake** of norepinephrine, dopamine, and serotonin leading to their accumulation in the synaptic spaces with profound **CNS stimulation**.
- Adverse effects: similar to amphetamine
- Manifestations of cocaine toxicity is managed by benzodiazepines.

MIXED-ACTING SYMPATHOMIMETIC DRUGS

Ephedrine

- Ephedrine is a **plant alkaloid** effective orally and, unlike catecholamines, penetrates the brain and can produce **CNS stimulation**.
- Ephedrine acts by **both**:
  – Release of norepinephrine from nerve endings.
  – Direct stimulation of **α and β** receptors (weak and prolonged).
- **Tolerance** develops to ephedrine after continuous administration.

Therapeutic uses

– Ephedrine is used as bronchodilator and CNS stimulant, but its clinical use is now **declining** because of the availability of better, more potent agents with fewer side effects.
– **Pseudoephedrine** is one of the four isomers of ephedrine. It is present in many nasal decongestant mixtures.

Chronic orthostatic hypotension

On standing, venous return is reduced by the effect of gravity. Normally, BP decrease is prevented by reflex sympathetic activation with increased HR, and peripheral VC.

Impairment of autonomic reflexes that regulate BP can lead to chronic orthostatic hypotension. This might be caused by drugs that impair autonomic function (e.g., tricyclic antidepressants and α blockers), diabetes, and autonomic neuropathy.

Drugs that activate **α1** receptors (e.g. **Midodrine)** can be used for this indication. **Ephedrine** can be also used (rarely).

Table 4. Selected therapeutic uses of adrenoceptor agonists (sympathomimetics)

Clinical condition	Agonist	Receptor
Cardiac arrest	Epinephrine	β1 – α1
Anaphylactic shock	Epinephrine	β2 – α1
Shock (most types)	Dopamine	D1 - β1
Cardiogenic shock	Dobutamine	β1
Chronic orthostatic hypotension	Midodrine, phenylephrine	α1
Bronchial asthma	Salbutamol, terbutaline, salmetrol	β2
Premature uterine contractions	Ritodrine	β2
Running nose (rhinitis)	Oxymetazoline, xylometazoline	α1
ADHD	Methylphenidate	?
Narcolepsy	Modafenil	?

Part 3: Adrenergic receptor antagonists

These drugs interact with either α- or β-adrenoceptors to prevent or reverse the actions of endogenously released catecholamines or exogenously administered sympathomimetics.

α- ADRENERGIC BLOCKERS

- **Non-selective α-receptor blockers:** phenoxybenzamine, phentolamine
- **Selective α1-receptor blockers:** prazosin , terazosin, doxazosin
- **Selective α2-receptor blockers:** yohimbine
- **The ergot alkaloids.**

1. Non-selective α- blockers: Phenoxybenzamine

- Phenoxybenzamine is a noncompetitive, **irreversible** antagonist at both **α1 and α2** receptors. It binds **covalently** with α receptors, resulting in **long-lasting** blockade (15 –50 h).
- Blockade of α receptors leads to **orthostatic hypotension** and reflex tachycardia.

Therapeutic uses

- **Management of pheochromocytoma**

– Phenoxybenzamine or phentolamine are used for long-term management of inoperable tumors.

– β-receptor antagonists are often given after α-blockers to prevent the cardiac effects of excessive catecholamines (see box).

Adverse effects

– Orthostatic hypotension and reflex tachycardia.
– Impairment of ejaculation.
– Miosis.

2. Selective α1- blockers: Prazosin, terazosin, doxazosin, tamsulosin

- Prazosin is the prototype drug.
- All of these agents decrease peripheral resistance and lower arterial BP by:
  – α1- receptor blockade.
  – Direct VD of both arterial and venous smooth muscles.
- They cause minimal changes in COP, RBF, and the GFR.
- They don't trigger reflex tachycardia by the same degree as the non-selective blockers.
- They improve plasma **lipid profile** and decrease LDL and TGs.
- Doxazosin has the longest duration of action (22 h).

Pheochromocytoma

It is tumor of the adrenal medulla that secretes excess catecholamines → headache, hypertension, palpitations, sweating, and dyspnea. 10% of the tumors are malignant.

Diagnosis:
- CT scan.
- High levels of VMA in urine

Treatment:
- Surgical excision of the tumor.
- Combined **α and β lockers** to block all adrenergic receptors:
  – Phenoxybenzamine 100 mg /day + propranolol 50 mg/day.
  – Start first with phenoxybenzamine to control BP then add β-blocker.
  – **If α-blockers are used alone**, the elevated catecholamines will act on unopposed β-receptors leading to severe palpitations, arrhythmia, etc.
  – **If β-blockers are used alone**, the elevated catecholamines will act on unopposed α-receptors leading to severe hypertension.
- **Labetalol** is a combined **α and β lockers** that could be used alone.

Therapeutic uses

- **Treatment of mild-to-moderate hypertension:** especially in patients with renal failure because it does not decrease RBF or GFR.
- **Treatment of congestive heart failure** because they decrease both the afterload and preload through combined arteriolo- and veno- dilatation (see CVS).
- **Benign prostatic hyperplasia (BPH) and impaired bladder emptying** because blockade of α1 receptors in smooth muscles of the bladder neck and prostate leads to decrease resistance to urine flow. The old drug prazosin is no longer recommended for this indication.

Tamsulosin is the most commonly used for treatment of **BPH** because:

- It has high affinity for α1A & α1D, the 2 receptor subtypes responsible for mediating smooth muscle contraction in prostatic tissue.
- It has little effect on standing BP compared with other α1-blockers.

Salt and water retention induced by BP lowering drugs

- It occurs as a compensatory response after long duration of antihypertensive therapy in the form of ankle edema and slight weight gain.
- Hypotension leads to reflex stimulation of the renin-angiotensin-aldosterone system which causes fluid retention.
- Diuretics are often prescribed with BP lowering drugs to minimize this effect.

Adverse effects

- **First dose hypotension (syncope)**
  - Occurs more frequently with **prazosin**. It starts 30-90 min after the first dose.
  - It occurs more frequently in salt and water depleted patients.
  - Prevention: start with a small dose at bedtime then increase the dose gradually.
- **F**luid retention (salt and water retention): (see box).
- **F**alse positive test for antinuclear factor of rheumatoid arthritis.
- α- blockers can worsen incontinence in women with pelvic floor pathology.

3. Selective α2- blockers: Yohimbine

- Selective presynaptic **α2-blocker** that leads to increase norepinephrine release.
- It is sometimes used as **aphrodisiac** (enhance sexual desire) without clinical evidence.

4. The ergot alkaloids

Chemistry and pharmacokinetics

- Ergots are a wide variety of compounds that are produced by the fungus *Claviceps purpurea.* These agents have a strong structural similarity to norepinephrine, dopamine, and serotonin.
- They may be natural or semi-synthetic:

Natural alkaloids	Semi-synthetic alkaloids
▪ Ergotamine ▪ Ergometrine ▪ Ergotoxine: a mixture of three other alkaloids. It is very toxic and not used clinically.	▪ Dihydroergotamine ▪ Methylergometrine ▪ Dihydroergotoxin ▪ Bromocryptine

- Ergots may be administered parenterally, rectally, or orally, and vary widely in their degree and speed of absorption.
- The absorption of ergotamine is increased by **caffeine**.
- Ergots are extensively metabolized to compounds of varying activity and half-life.

Mechanism and pharmacological effects

- Ergots act as **agonist, antagonist** or **partial agonists** at three receptor types: α-, dopamine, and serotonin receptors.
- The pharmacologic use of ergots is determined by the relative effect of each member on these receptors.

Drug	Receptor	Main effect	Main uses
Ergotamine	Partial agonist at α- and 5-HT receptors	Direct VC with greater effect on cerebral BVs	Acute migraine attacks
Methlyergometrine	α-receptors agonist	Uterine smooth muscle contraction	Postpartum hemorrhage
Dihydroergotoxin	α-receptors antagonist	VD with greater effect on cerebral BVs	Senile cerebral insufficiency
Bromocryptine	Dopamine agonist	Pituitary and nigrostriatal pathway	Suppress lactation and ttt of parkinsonism

Therapeutic uses

- **Ergotamine: acute migraine**
  - The major effect of ergotamine is cerebral VC by a direct action; it reverses the rebound VD that is the probable cause of pain.
  - It should be given at the start of aura because it has slow onset. It is better to be combined with **caffeine** because caffeine increases its absorption.
  - If given before aura (e.g. for prophylaxis), it can induce cerebral VC and precipitates the acute attack (i.e. contraindicated).
  - The VC induced by ergotamine is long-lasting and cumulative; therefore, patients must not take more than 6 mg of the oral preparation for each attack.

- **Methylergometrine: postpartum hemorrhage**
  - It causes prolonged and forceful contraction of uterine smooth muscles**.**
  - Ergots should **not be used to induce labor**. It should be given at the time of placenta delivery (3rd stage of labor) and never before that. If it is given before delivery of the placenta, it causes severe spasm of uterine smooth muscles and retained placenta.

- **Bromocriptine: hyperprolactinemia**
  - Bromocriptine is a dopamine receptor agonist that causes inhibition of prolactin secretion *(high prolactin levels can induce infertility and amenorrhea in women).*
  - It is used to suppress normal lactation and as a dopamine alternative in Parkinson's disease

- **Dihydroergotoxin:** used as cerebral vasodilator in senile cerebral insufficiency.

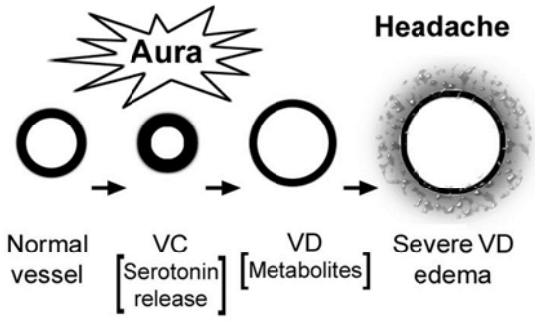
Adverse effects of ergot alkaloids

- Nausea and vomiting due to stimulation of CTZ.
- High doses cause VC of small arterioles of fingers leading to cold hands and even gangrene (ergotism).
- VC of coronary artery with anginal pain.
- Uterine contraction and abortion if given during pregnancy.

MIGRAINE AND SOME DRUG TREATMENTS

Migraine is severe unilateral periodic headache characterized by:

- **The stage of aura:** occurs in 15-30% of cases. Sudden release of serotonin (and other mediators) of unknown etiology causing VC of cerebral BV → visual, olfactory or auditory hallucinations.
- **The stage of pain:** prolonged VC leads accumulation of waste metabolites → severe VD → perivascular edema and severe headache.



Pathophysiology of migraine

The exact aetiology of migraine is not clearly understood but the serotonin hypothesis is widely accepted

Drugs used in the acute attack

- **Ergotamine** and **dihydroergotamine** (see before).
- **Triptans: sumatriptan, zolmitriptan**
  - They are agonists at **5-HT$_{1D}$** and **5-HT$_{1B}$** receptors.
  - Activation of **5-HT$_{1D}$** receptors inhibits inflammation of meninges, pain transmission, and release of VD substances e.g. calcitonin gene-related peptide in trigeminal neurons. Activation of **5-HT$_{1B}$** receptors causes VC of the dilated cerebral vessels. About 50%–80% of patients report relief from pain within 2 hours after oral administration.

- 5-HT_{1B} activity can cause **coronary spasm** so; these drugs are contraindicated in patients with ischemic heart disease (IHD).
- Like ergotamine, they are also **contraindicated** for prophylaxis of migraine or in combination with ergotamine because severe hypertension and coronary spasm may occur.

Drugs used for prophylaxis

- Propranolol: the most commonly used drug for prophylaxis.
- Ca^{2+} channel blockers: verapamil (unclear mechanism).
- Clonidine: (unclear mechanism).
- Tricyclic antidepressant (TCA) drugs.

β- ADRENERGIC BLOCKERS

The β-receptor–blocking drugs differ in their relative affinities for β1 and β2 receptors; however, the **selectivity is dose-related** and tends to diminish at higher doses.

- **Non-selective β-blockers:** e.g. propranolol, pindolol, timolol, sotalol, nadolol
- **Cardio-selective β_1-blockers:** e.g. atenolol, metoprolol, bisoprolol, nebivolol.
- **β-blockers with additional VD action:** e.g. dilevalol, carvedilol

  N.B. the VD action comes from either: blocking the vascular **α1** receptors; increasing PGE_2 and PGI_2 synthesis; or by release of endothelial NO.

Chemistry and pharmacokinetics

- **Propranolol** is the prototype β-adrenoreceptor antagonist.
- β-blockers are absorbed well after oral administration, many have **low bioavailability** because of extensive first-pass metabolism.
- **Lipophilic** β-blockers (e.g. **propranolol**) can pass readily to the CNS and are cleared by hepatic metabolism. **Hydrophilic** β-blockers (e.g. **atenolol**) have limited penetration to the CNS and are excreted primarily by the kidney with little hepatic metabolism.
- β-blockers which undergo **hepatic** metabolism usually require **multiple** daily dosing. Drugs eliminated via the **kidney** are suitable for **once** daily administration.

Mechanism and pharmacological effects

CVS effects

- They block cardiac β1 receptors and **decrease all cardiac properties** (↓ contractility and COP, ↓ A-V conduction **"bradycardia"**, ↓ excitability, and automaticity).

- They **block the β2-mediated VD** in peripheral vessels leading to ↓ blood flow to most tissues.
- **They decrease blood pressure through:**
  - ↓↓ COP by their –ve inotropic and chronotropic effects.
  - ↓↓ renin release from the kidney (β1).
  - ↓↓ norepinephrine release and central sympathetic outflow (by blocking presynaptic β2).
  - They cause resetting of baroreceptors to a lower level (see before).
  - Some β-blockers block also vascular α1 receptors.
  - Some β-blockers enhance synthesis of vasodilator PGE_2 and PGI_2.

Respiratory

- β-blockers produce **bronchospasm** as a result of β2-receptor blockade; this effect is more significant in **asthmatic patients**.
- Even **selective** β1 blockers can interact with β2 receptors in high doses and produce bronchospasm, especially in asthmatic patients.

Eye

- ↓ IOP by decreasing aqueous humor secretion from the ciliary epithelium (**timolol** and **betaxolol** have excellent effect).
- Sufficient timolol can be absorbed after topical application to increase airway resistance and decrease HR and contractility.

Metabolic effects

- Inhibition of **glycogenolysis** in the liver (β2) leading to aggravation of hypoglycemic effect of insulin and other hypoglycemic drugs.
- ↑ plasma K^+ (hyperkalemia) in **patients with renal failure**.
- ↑ plasma triglycerides and ↓ HDL.

CNS

- Antianxiety effects.
- Night mares, vivid dreams, and depression.
- Sexual dysfunction through combined central and peripheral mechanisms.

Skeletal ms

- ↓ essential **tremors** due to blocking of β2 in skeletal muscles.

Other specific properties

- **Propranolol** has <u>local anesthetic</u> (membrane stabilizing) action i.e. it can inhibit excitability of the cardiac muscle.
- **Pindolol** is a <u>partial agonist</u> i.e. it doesn't cause excessive bradycardia.
- **Esmolol** is <u>ultrashort acting</u> (t1/2 = 10min) because of extensive hydrolysis by plasma esterases; it is administered by i.v. infusion to control arrhythmia during surgery and emergency situations.
- **Labetalol** blocks β-receptors and α1-receptors (<u>mixed blocker</u>).

- **Carvedilol** has additional antioxidant action.
- **Nebivolol** is the most selective β1 blocker.

Therapeutic uses

- **Treatment of hypertension:** (see the mechanisms above). All beta-blockers, irrespective of their properties, lower BP to a similar extent.

- **Ischemic heart disease (classic angina** and **acute MI)**
  - They decrease contractility, HR, and systolic BP, thus decrease myocardial work and O_2 demand (in acute myocardial infarction (AMI), β-blockers given within 6-12 h can decrease the infarct size).
  - They increase the diastolic (coronary) filling time.
  - They cause redistribution of blood to the ischemic (subendocardial) regions.
  - β-blockers improve myocardial metabolism through metabolic switching from *fat* utilization to *carbohydrates* utilization (cytoprotective effect).

- **Cardiac arrhythmias** (especially thyrotoxic and supraventricular arrhythmia).
  - They decrease A-V conduction, lengthen the refractory periods of the SA node, and suppress automaticity.
  - Propranolol decreases excitability through its membrane stabilizing action.
  - Acute arrhythmia during **surgery** is treated by i.v. **esmolol**.

- **Hypertrophic obstructive cardiomyopathy**
  - It is a congenital thickening of the ventricular wall and interventricular septum. It is the most common cause of sudden death in young athletes. Thickening of the interventricular septum impairs blood flow through the aortic outlet especially during exercise.
  - Drugs having –ve inotropic effect such as β-blockers and verapamil decrease HR and contractility, thus decrease the outflow tract resistance. Drugs with +ve inotropic effects (e.g. digoxin) have the opposite effect.

- **Hyperthyroidism:** propranolol is used to control tachycardia, anxiety, and tremors due to sympathetic overactivity in hyperthyroidism. It also prevents peripheral conversion of T_4 into T_3.

- **Esophageal varices due to liver cirrhosis:** propranolol is used to decrease portal and hepatic blood flow through combined decrease of COP and inducing VC in the splanchnic vascular bed (through an unopposed α-action).

- **Open angel glaucoma:** topical timolol or betaxolol ↓ aq humor secretion.

- **Other uses:** pheochromocytoma (must be combined with alpha-blockers); and prophylaxis of migraine (propranolol has an unclear mechanism).

Adverse effects

- Tiredness and **fatigue** (the most common side effect) due to reduced COP and block of β2-mediated VD in skeletal muscles (mainly non-selective agents).
- **Bradycardia** and impairment of myocardial contractility, so they can precipitate **heart failure** or **heart block** in patients with compromised cardiac function.
- **Bronchospasm** in susceptible individuals due to blockade of β2-receptors which mediate dilation in the bronchi. Asthma is an absolute contraindication for **all** beta-blockers.
- Aggravation of **peripheral ischemia** and cold extremities (mainly non-selective agents). (selective β-blockers are the preferred class if there is associated peripheral vascular disease).
- In diabetic patients, β-blockers (mainly non-selective) can potentiate the **hypoglycemic effect** of insulin and oral hypoglycemic drugs (because they block glycogenolysis), and **mask tachycardia & tremors** resulting from severe hypoglycemia.
- **CNS effects:** vivid dreams, night mares, and depression.
- **Sudden withdrawal** can increase the risk of **angina** and **arrhythmias** due to adrenoceptor "supersensitivity". Gradual withdrawal is recommended.

Heart block

Heart block means block of the electrical conduction at any point in the conducting system e.g. SA nodal block, AV nodal block, or bundle branch block.

N.B.

Excessive **myocardial depression** caused by overdose of β-blockers can be reversed by **i.m. glucagon**. This is because β-blockers decrease intracellular cAMP making all β-agonists acting through cAMP is useless. Glucagon increases **contractility** by a mechanism unrelated to cAMP.

Contraindications

- **Absolute contraindications**
  - Bronchial asthma.
  - Any degree of heart block.
  - Prinzmetal's (vasospastic) angina (see CVS).
  - Sudden withdrawal after long-term use.
- **Relative contraindications**
  - Acute – or severe chronic heart failure.
  - Peripheral vascular diseases (PVD).
  - Diabetes mellitus.
  - In athletes involved in strenuous sports because beta-blockers can interfere with the ability to perform strenuous physical activities.

Part 4: Sympathoplegic drugs

CENTRALLY-ACTING SYMPATHOPLEGIC DRUGS

1. Alpha-methyldopa

Mechanism and pharmacological effects

In the CNS, α-methyldopa competes with dopa for *dopa decarboxylase* enzyme leading to formation of α-methylnorepinephrine, (and also α-methyldopamine), which is a false transmitter. α-methylnorepinephrine stimulates **central α2** receptors leading to reduced central sympathetic outflow and decreased BP.

Therapeutic uses

Methyldopa is the drug of choice to treat arterial **hypertension in pregnancy** because of its long and reliable track record.

Adverse effects

- The most common side effect is **sedation, nightmares,** and **mental depression** due to central deficiency of norepinephrine.
- Mild hyperprolactinemia and extrapyramidal manifestations due to central deficiency of dopamine.
- **Positive Coombs test** and autoimmune hemolytic anemia.
- Autoimmune hepatitis is **rare**.

2. Clonidine

Mechanism and pharmacological effects

- Clonidine is a **central α2-receptor agonist** leading to decreased central sympathetic outflow and reduction in the total peripheral resistance.
- Reduction of BP is **not** associated with changes of the RBF or GFR.

Therapeutic uses

- It is mainly used in the management of **hypertension complicated by renal disease.**
- To **reduce anxiety** accompanying **opiate withdrawal** or surgical operations.

Adverse effects

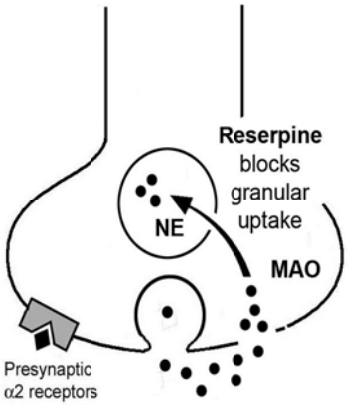
- **S**edation and dry mouth (central effect).
- **S**udden withdrawal of the drug can lead to **rebound hypertension**.
- **S**alt and water retention so it is usually combined with diuretics.

ADRENERGIC NEURON BLOCKERS

Reserpine

Mechanism and pharmacological effects

- Reserpine is a plant alkaloid that blocks **vesicular uptake** of the neurotransmitters norepinephrine, dopamine, and serotonin in both central and peripheral neurons, as well as adrenal medulla.
- These transmitters accumulate in the neuronal cytoplasm and are degraded by MAO enzyme, leading finally to **depletion** of the nervous system from these biogenic amines.
- The effect of reserpine is **slow** and **persists** for many days after discontinuation.



Therapeutic uses

Treatment of mild-to moderate hypertension; however, it is now not considered among the first or second line drugs because of numerous adverse effects.

Adverse effects

- The most important side effect is **sedation, nightmares,** and **mental depression** (2%) due to central depletion of both norepinephrine and serotonin.
- Hyperprolactinemia and extrapyramidal manifestations (parkinsonism) may occur due to central depletion of dopamine.
- GIT symptoms (abdominal cramps, mild diarrhea, increase HCl) are common due to overpredominance of parasympathetic activity.

Part 5: Parasympathomimetic drugs (Cholinomimetics)

- The parent compound of all cholinomimetic drugs is **acetylcholine**.
- **ACh is the natural neurotransmitter in the following sites:**
  - All autonomic ganglia whether sympathetic or parasympathetic.
  - Parasympathetic nerve endings to involuntary organs and exocrine glands.
  - Sympathetic nerve endings to thermoregulatory sweat glands.
  - Sympathetic nerve endings to adrenal medulla.
  - Skeletal muscle motor end plate.
  - Certain tracts within the CNS
- ACh acts on both **muscarinic** and **nicotinic** receptors to produce all the effects listed in **table 1**, and **table 3** (see before).
- ACh is **not used clinically** because: (1) it has very short duration of action (seconds) due to rapid hydrolysis by AChE enzyme; and, (2) it lacks selectivity.
- **Cholinomimetic drugs** are drugs that produce effects similar to ACh or cholinergic nerve stimulation, but with **more selectivity** and **fewer side effects** than ACh.

Classification of cholinomimetic drugs

Direct-acting cholinomimetics	Indirect-acting cholinomimetics
They act by **direct stimulation** of cholinergic receptors	They act by **inhibition of AChE enzyme** leading to accumulation of ACh.
■ **Muscarinic agonists** Bethanecol, carbachol Pilocarpine, cevimeline	■ **Reversible ChE inhibitors:** Physostigmine, neostigmine, pyridostigmine, donepezil
■ **Nicotinic agonists** Nicotine, lobeline	■ **Irreversible ChE inhibitors:** Organophosphate compounds

DIRECT-ACTING PARASYMPATHOMIMETICS

Muscarinic agonists:

Pharmacological effects:

CVS
- ↓ AV conduction and HR (M2).
- VD of all vascular beds through release of EDRF (M3).

Respiratory effects
- Contraction of bronchial smooth muscle (M3).
- ↑ bronchial secretions (M3).

Eye	▪ **Miosis** due to contraction of constrictor pupillae muscle (M3). ▪ Accommodation for **near vision** due to contraction of ciliary muscle (M3). ▪ ↓ IOP (contraction of the ciliary muscle causing opening of the trabecular meshwork and facilitates drainage of aq humor).
GI tract	▪ ↑ motility and relaxation of sphincters (M3). ▪ Salivation (M3) and increase HCl secretion (M1).
Urinary tract	▪ Contraction of bladder smooth muscles (M3). ▪ Relaxation of sphincters (M3).
Exocrine gld	▪ ↑ all exocrine secretions, salivation, lacrimation, sweating, etc.

1. Carbachol

- It is choline ester but resistant to hydrolysis by AChE enzyme.
- It stimulates both **muscarinic** and **nicotinic** receptors.
- It is used as **local eye drops** to ↓ IOP in **glaucoma**. It contracts the ciliary ms causing opening of the trabecular meshwork and facilitates drainage of aq humor.

2. Bethanecol

- It is a choline ester but resistant to hydrolysis by AChE enzyme, so it has long duration of action (2-3 h) as compared to Ach.
- It stimulates **muscarinic** receptors with **no activity on nicotinic receptors**.
- It is used to reverse **post-operative urine retention** and **paralytic ileus** (in absence of organic obstruction).

N.B.

- Bethanechol is administered orally or s.c., **not by i.v. or i.m.,** because parenteral administration may cause **cardiac arrest**.
- Bethanechol is contraindicated to treat urine retention due to **mechanical obstruction** of the bladder or intestine because increasing contraction against a closed outlet can lead to **rupture** of the viscus.

3. Cevimeline and pilocarpine

- Cevimeline is synthetic drug – pilocarpine is a natural plant alkaloid.
- Both drugs act as **muscarinic agonists** with **no nicotinic effects**.
- Both drugs can be given orally to **increase salivary secretion** and decrease symptoms of dry mouth (xerostomia) associated with **Sjögren syndrome.**
- Pilocarpine is used as **local eye drops** to ↓ IOP in **glaucoma**.

Adverse effects of muscarinic agonists

– Most important side effects include nausea, vomiting, sweating, salivation, **bronchoconstriction**, hypotension, and diarrhea; all of which can be blocked by **atropine**.

Contraindications of muscarinic agonists

– Peptic ulcer
– Bronchial asthma
– Heart block.

Nicotinic agonists:

1. Nicotine

- It is a component of cigarette smoke. It is a **poison** with many adverse effects and **no therapeutic** benefit.
- The overall effects of nicotine are complex and result from **mixed** stimulation and inhibition of all autonomic ganglia:
  - ***Small doses*** stimulate autonomic ganglia leading to hypertension, tachycardia, increase GIT peristalsis, increase HCl secretion, and CNS stimulation.
  - ***Toxic doses*** lead to hypotension and CNS depression due to ganglion blockade.
- Nicotine is addictive substance. **Transdermal patches** containing nicotine are used to help smokers stop smoking.

2. Varenicline

- It is nicotinic receptor **partial agonist** used for smoking cessation.
- **Headache** and nausea are the most common adverse effects.
- Contraindicated in **pregnancy** and breast feeding.

How smoking elevates blood pressure?

- Nicotine stimulates sympathetic ganglia and suprerenal medulla causing release of catecholamines with subsequent VC and increase HR.
- Nicotine stimulates ADH (vasopressin) release from posterior pituitary.
- Tobacco smoke cause vascular endothelial dysfunction and accelerates atherogensis.

Smoking cessation

Patients should be offered **nicotine replacement therapy (NRT)** or **varenicline**. The two prescriptions should not be combined together.

Nicotine replacement therapy

These are nicotine containing transdermal patches. It should be started 2 weeks before the target date to stop.

Varenicline

- It should be started 1 week before the target date to stop. The recommended course of treatment is 12 weeks.

INDIRECT-ACTING PARASYMPATHOMIMETICS (Cholinesterase inhibitors)

Mechanism and pharmacological effects

- Indirect-acting parasympathomimetics **inhibit AChE enzyme** resulting in accumulation of ACh and stimulation of both **muscarinic** and **nicotinic** receptors.
- They are classified, according to nature and duration of **AChE inhibition,** into **reversible** and **irreversible** inhibitors.

Reversible AChE inhibitors:

They interact with AChE enzyme by making **reversible bond** allowing duration of inhibition lasting from minutes to hours.

1. Physostigmine

- Natural plant alkaloid (tertiary amine) that is well-absorbed from the GIT and **can pass to CNS**.
- It can reversibly inhibit AChE enzyme for 3-4 hours, leading to:
  - ***Muscarinic effects:*** hypotension, bradycardia, salivation, lacrimation, increased GIT peristalsis (diarrhea and colic), miosis, etc.
  - ***Nicotinic effects:*** skeletal muscle contraction.
  - ***Central effects:*** headache, insomnia, excitation, and convulsions.

Therapeutic uses

- Because of lack of selectivity and harmful CNS effects, it is usually used as **local eye drops** to produce miosis and treat chronic **glaucoma**.
- Physostigmine can be used to reverse the central and peripheral manifestations of **atropine poisoning**.

2. Neostigmine

- Synthetic drug (quaternary amine) that is **poorly absorbed** from the GIT and **cannot pass to CNS**.
- It is similar to physostigmine in mechanism and effects but it has **no CNS actions**.

Therapeutic uses

- To reverse postoperative **urine retention** and **paralytic ileus**. It is contraindicated if there is **mechanical obstruction** (to avoid rupture of the bladder or intestine).

- To reverse postoperative **muscle paralysis** resulting from the use of non-depolarizing neuromuscular blockers.
- Treatment of **myasthenia gravis:**
  - Neostigmine not only increases ACh level in the neuromuscular junction but also can **directly stimulate** nicotinic receptors at the motor end plate.
  - **Atropine** could be given with neostigmine to block the unwanted muscarinic effects caused by excessive ACh.

3. Pyridostigmine

- Reversible AChE inhibitor similar to neostigmine.
- It is more preferred than neostigmine in the chronic treatment of **myasthenia gravis** because:
  - It has more selective action on neuromuscular junction (fewer unwanted muscarinic effects).
  - It has longer duration of action than neostigmine.

4. Edrophonium

- It acts as the same of neostigmine and pyridostigmine but has very short duration of action (5-15 minutes).
- It is used in the **diagnosis of myasthenia gravis** and to differentiate between muscle weakness due to insufficient treatment of myasthenia, or due to excessive treatment with AChE inhibitors (Tensilon test).

Myasthenia gravis

- Myasthenia gravis is an **autoimmune disease** in which antibodies complex with nicotinic receptors at the neuromuscular junction to cause skeletal muscle weakness
- AChE inhibitors, such as **pyridostigmine**, are used to increase ACh levels at the neuromuscular junction to fully activate the remaining receptors.
- Myasthenia gravis can be diagnosed using the **Tensilon test**, which can also assess the adequacy of treatment with AChE inhibitors.

Alzheimer's disease

- Alzheimer's disease is chronic degenerative disease characterized by progressive impairment of memory and cognitive functions.
- Pathologic changes include increased deposits of amyloid β peptide and abnormal protein (tau protein) in the cerebral cortex, leading to cerebral vascular lesions, and progressive loss of **cholinergic neurons**.
- Although evidence for the benefit of AChE inhibitors is statistically significant, the clinical benefit from these drugs is mild and temporary.

- **Tensilon test**: small doses of **edrophonium** improve muscle strength in untreated patients with myasthenia, but worsen muscle weakness if it was due to excessive dose of AChE inhibitors (excessive ACh stimulation at the neuromuscular junction results in muscle weakness due to maintained depolarization).

5. Donepezil and rivastigmine

- They are AChE inhibitors that act more selectively on **central AChE** enzyme.
- They are used to increase ACh levels in the CNS and thus improve memory and cognitive deficit associated with **Alzheimer's disease** (see box).

Irreversible ChE inhibitors: Organophosphate compounds

- They include:
  - **Drugs:** echothiophate eye drops
  - **Insecticides:** parathion and malathion
  - **Nerve gases:** sarin and soman

- Organophosphates are **highly lipid soluble** and rapidly absorbed by all routes including the **skin**. Their **CNS** penetration is rapid and high.
- They interact with AChE enzyme by making **irreversible (covalent) bond** (i.e. phosphorylation of the enzyme).
- As time passes, the strength of the bond increases, (a process called **"aging"**), and AChE becomes **irreversibly** inhibited. *(With most types of organophosphates, 50% of the enzyme undego aging after 3 hrs and 95% after 12 hrs).*
- Once AChE is inhibited, ACh accumulates throughout the nervous system, causing muscarinic and nicotinic symptoms.
- **Echothiophate** is the only non-absorbable organophosphate. It is available as miotic **eye drops** for **glaucoma**. Its effect in the eye lasts for weeks.

Manifestations of organophosphate toxicity:

- **CVS:** hypotension, bradycardia, sweating.
- **Respiratory:** bronchospasm, increase bronchial secretions, respiratory ms paralysis.
- **GIT:** abdominal colic, diarrhea, and salivation.
- **Eye:** severe miosis *(pinpoint pupil)*, lacrimation.
- **CNS:** hallucinations, convulsions, and coma.
- **Skeletal ms:** twitches and fasciculation.
- **The cause of death** is respiratory failure (blocked airway, paralyzed respiratory ms & inhibited RC).

The DUMBELS syndrome:

D: Diarrhea & colic.
U: Urination.
M: Miosis.
B: Bradycardia & Bronchospasm
E: Emesis (vomiting) Excitaion of CNS
L: Lacrimation.
S: Salivation & Sweating. Skeletal ms twitches

Management

- Ensure patent airway and artificial respiration.
- Gastric lavage and skin wash to remove the toxin.

- Intravenous normal saline to raise BP.
- **The triad: atropine – pralidoxime – diazepam**

Atropine (2 mg i.v. bolus)

- Atropine is non-selective muscarinic blocker and can cross BBB to block all muscarinic manifestations of excess ACh **centrally** and **peripherally.**
- Check pulse and BP after 5 min; if no response, repeat the dose of atropine till the HR is > 80 bpm and systolic BP > 80 mmHg.
- The patient should be maintained atropinized for 24-48 hrs because organophosphates are highly lipid soluble. So, it may dissolve in body fat and released again over time.

Pralidoxime (PAM; 2 gm i.v. over 20-30 min)

- It is also available as ready-to-use autoinjector.
- If given early (before aging), it can **reactivate** (dephosphorylate) AChE enzyme especially at the neuromuscular junction.
- Pralidoxime is only effective in organophosphate toxicity (i.e. it does not have an effect if AChE enzyme is carbamylated, as occurs with neostigmine or physostigmine).

Diazepam (10 mg i.v. or i.m.): to control convulsions.

Table 5. Selective therapeutic indications of parasympathomimetics

Clinical condition	Drug	Receptor
Postoperative urine retention and paralytic ileus	Bethanechol (direct) Neostigmine (indirect)	M3 M & N
Glaucoma	Pilocarpine, Carbachol, physostigmine	M3 M & N
Xerostomia	Cevemeline	M3
Alzheimer's disease	Donepezil, rivastigmine	M & N
Myasthenia gravis	Neostigmine, pyridostigmine	Nm
Diagnosis of myasthenia	Edrophonium	Nm
Atropine toxicity	Physostigmine	M & N

Part 6: Muscarinic antagonists

Actions and chemical structure

They are either tertiary amine alkaloids or quaternary amines:

- **Plant alkaloids:** atropine is found in *Atropa belladonna* and scopolamine (hyoscine) is found in *Hyoscyamus niger.* They are tertiary amines (i.e. well absorbed and can pass to **CNS**).
- **Synthetic derivatives:** are either tertiary or quaternary amines (limited **CNS** penetration):
  - Drugs used mainly as **bronchodilators:** Ipratropium
  - Drugs used mainly as **antispasmodics:** Hyoscine butylbromide
  - Drugs used mainly to **decrease HCl secretion:** Pirenzepine
  - Drugs used mainly for **genitourinary system:** Oxybutynin, tolterodine
  - Drugs used mainly as **mydriatics:** Homatropine, tropicamide
  - Drugs used mainly to treat **parkinsonism:** Benztropine

Mechanism and pharmacological effects

Muscarinic-receptor antagonists are **competitive antagonists** of ACh at all muscarinic receptors.

CVS effects	▪ They block M2 receptors in the SA node and **increase HR**. ▪ **No significant effect on the force of contraction** because there are no muscarinic receptors, or parasympathetic innervation of the ventricles. ▪ Blockade of vascular M3 receptors has **no significant clinical value.** ▪ High doses cause **toxic VD** in the facial blush area **(atropine flush)** which is not related to the antagonistic action.
Respiratory	▪ Bronchodilatation and decrease mucus secretion.
GIT	▪ Decrease salivation and HCl secretion. ▪ Decrease motility (antispasmodic action).
Urinary bladder	▪ Relaxation of the bladder smooth muscles and contraction of the sphincters leading to **urine retention**.
Sweat glands	▪ Blocking of muscarinic receptors in thermoregulatory sweat glands (cholinergic) leading to **dry skin** and elevation of body temperature **(atropine fever)**. ▪ **Children** are more sensitive to this effect.
Eye	▪ Passive **mydriasis** due to paralysis of constrictor pupillae muscle.

- **Cycloplegia** (paralysis of ciliary muscle) leading to loss of accommodation for near vision.
- Increase **IOP** due to mydriasis (decrease aqueous humor drainage).

CNS

- **Tertiary amines** can produce sedation, amnesia, delirium, and hallucinations.

Therapeutic uses

CVS:

- **Bradycardia:** parenteral **atropine** is the standard drug for most cases of bradycardia including **reflex** bradycardia caused by vasopressor drugs.

Respiratory:

- **Bronchial asthma: Ipratropium** is a quaternary amine. It has greater selectivity for the bronchial tissue and **limited CNS effects**. It is given by inhalation to dilate the bronchi and reduce secretions in asthma and chronic obstructive pulmonary disease (COPD).
- **Preanesthetic medication:** Preanesthetic injection of **atropine** is used in order to:
  - Prevent bronchoconstriction and reduce bronchial secretions caused by excessive vagal stimulation during anesthesia.
  - Protect the heart from excessive vagal tone (bradycardia) occurred during anaesthesia.

GIT disorders:

- **Peptic ulcer: pirenzepine** has greater selectivity for blocking M1 receptors in the stomach and reduce HCl secretion; however, it is now **rarely used** because of the availability of new and more potent drugs.
- **Diarrhea:** the classic combination of **atropine** with **diphenoxylate**, (a congener of meperidine), is available under many names (e.g, Lomotil). They decrease hypermotility and secretions.
- **Abdominal colic:** e.g. hyoscine butylbromide (Buscoban).

Urinary disorder:

- **Acute cystitis: oxybutynin** is used to decrease bladder spasm and urinary urgency associated with inflammatory bladder disorders.
- **Urine incontinence in adults: tolterodine** is a new muscarinic antagonist used for this indication because it has **greater selectivity** for bladder M3 receptors and has **long duration** of action.

Eye:

- **Funduscopic examination:** muscarinic antagonists are used as eye drops **(cyclopentolate; tropicamide)** to produce mydriasis and cycloplegia and facilitate retinal examination; however, **phenylephrine** (α-agonist) is preferred for simple fundus examination due to its **short duration**.
- **Iridocyclitis:** inflammation of the iris can cause adhesions between the iris and lens (synechia). Long acting **atropine** eye drops is used to produce complete cycloplegia and mydriasis (M3) to prevent this adhesion.

CNS:

- **Parkinson's disease: benztropine** has greater selectivity for blocking the muscarinic receptors in the **basal ganglia** and decrease the excitatory effect of ACh.
- **Motion sickness: scopolamine** (hyoscine) is the standard drug used for this indication. It blocks muscarinic receptors in the **vestibulocerebellar** pathway that are responsible partially for the nausea and vomiting.

Motion sickness

- It is a very common disturbance of the inner ear that is caused by repeated motion such as from the movement of a car or ship.
- Bizarre head movement affects the organs of balance and equilibrium (vestibulocerebellar apparatus) causing nausea and vomiting.
- Overactivity of **muscarinic receptors** is suspected to play an important role in this condition.

Other:

- **Organophosphate toxicity: atropine** is the standard drug (see before).

Adverse effects

- Blurred vision (due to mydriasis and cycloplegia).
- Rise of IOP (**glaucoma**).
- **Dryness** of all body secretions: dry mouth, dry skin, dry eyes, etc..
- **Urine retention** especially in patients with **senile enlarged prostate**.
- Tachycardia.
- **In children:** atropine **fever** (due to blockade of thermoregulatory sweating resulting in hyperthermia) and **flush** . Children are more sensitive to this effect.

Contraindications

- Narrow angle glaucoma
- Obstructive diseases of the GIT (e.g. pyloric stenosis), paralytic ileus, intestinal atony of the elderly, etc.
- Urine retention due to **senile enlarged prostate**
- It should be used with caution in children.

Part 7: Ganglion blocking drugs

- **Trimethaphan** and **mecamylamine** are competitive blockers of ACh at nicotinic receptors at both sympathetic and parasympathetic ganglia.
- Because of lack of selectivity and **numerous adverse effects**, they are **used rarely** in the clinical setting hypertensive emergencies).

Part 8: Neuromuscular blockers

	Non-depolarizing NMBs	Depolarizing NMBs
members	■ **Tubocurarine** (prototype) is rarely used clinically at this time ■ **Semisynthetic derivatives:** – Mivacurium – Atracurium and *Cis*atracurium – Vecuronium	■ **Succinylcholine** (It is ester of ACh)
Absorption and distribution	– All members are not absorbed orally because they are **polar** compounds (quaternary amines), they must be given **parenterally**. – All cannot cross BBB or placental barrier	
Metabolism	– Atracurium: spontaneous plasma hydrolysis. Breakdown products may cause **seizures.** – Vecuronium: liver.	– By plasma pseudo ChE enzyme
Duration	– Mivacurium: 10-20 min – Atracurium: 20-30 min – Vecuronium: 30 -40 min	– Few minutes.
Mechanism of action	– **Competitive block** of Ach at **Nm** receptors → muscle paralysis. – Muscle paralysis can be reversed by excess Ach (AChE inhibitors).	– **Depolarizing block** of **Nm** receptors → ms paralysis through **2 phases:** ▪ **Phase 1:** initial depolarization → transient ms contraction followed by paralysis due to maintained depolarization

<table>
<tr>
<td></td>
<td></td>
<td>(depolarization block).
▪ Phase 2: the muscle becomes repolarized again but remains insensetive to stimulation by Ach (i.e. it needs ↑ Ach to be stimulated) (desensitization block).</td>
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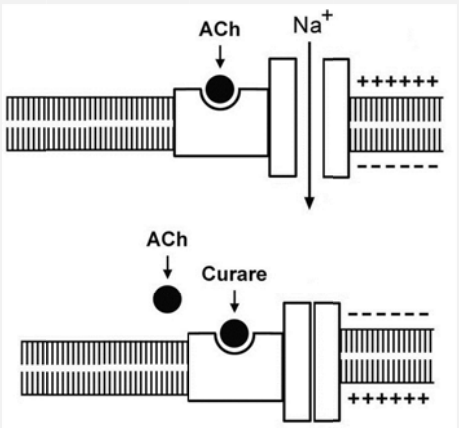
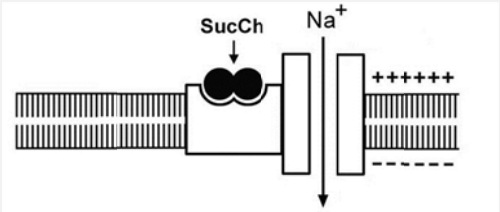
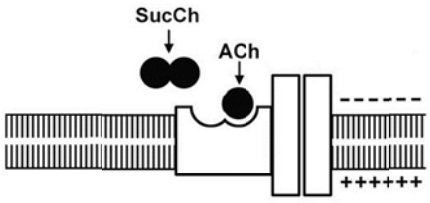
<td> 

Curare competitively blocks ACh Nm receptors and could be abolished by excess ACh.</td>
<td> 

Phase 1. Initial depolarization resulting in sudden and severe ms contraction


Phase 2. The membrane becomes repolarized again but remains insensetive to stimulation by Ach</td>
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<tr>
<td>Reversal of block</td>
<td>– Neostigmine can reverse the block by increasing Ach level at NMJ and displace competitive blockers from the receptors.</td>
<td>– Neostigmine increases muscle paralysis during phase 1 (due to increase muscle depolarization), but it can reverse the block in phase 2 (because the receptor is relatively insensetive and needs excess Ach to be stimulated).
– Fresh blood transfusion.</td>
</tr>
<tr>
<td>Therapeutic uses</td>
<td>– To induce sk ms relaxation during surgical operations.
– To control convulsions during electroconvulsive (ECT) therapy</td>
<td>– The same but succinylcholine is preferred for <u>short procedures</u> e.g. endotracheal intubation (has shorter duation).</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>– Histamine release leading to hypotension and</td>
<td>– Sudden rise of IOP due to contraction of the extraocular</td>
</tr>
</table>

	bronchospasm. – Respiratory paralysis in high doses.	muscles in phase 1. – **Acute hyperkalemia** (which may be dangerous and life-threatening). It is due to efflux of muscle K^+ during depolarization. – Postoperative muscle **pain.** – **Bradycardia** due to stimulation of cardiac muscarinic receptors (similar to ACh). – Prolonged **respiratory paralysis (apnea)** may result from **congenital deficiency of PsChE enzyme** (treaed by artificial respiraion and blood ransfusion).
C/I and precautions	– Bronchial asthma: why? – Myasthenia gravis. – With aminoglycosides or quinidine (they can aggravate ms paralysis).	– Glaucoma or recent eye surgery: why? – Congenital deficiency of PsChE enzyme: why?

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Review Questions

Mention the pharmacodynamic principles underlying the use of:

- Dopamine in shock.
- Adrenaline in acute anaphylactic shock.
- Ritodrine to delay premature labor.
- Sumatriptan in acute migraine.
- Ergometrine in postpartum hemorrhage.
- Tamsulosin in senile enlarged prostate.
- Propranolol (beta-blockers) in hypertension.
- Beta-blockers in obstructive cardiomyopathy.
- Alpha-methyldopa in hypertension of pregnancy.
- Neostigmine in myasthenia gravis.
- Pralidoxime (PAM) in organophosphate toxicity.
- Atropine before surgical operations.
- Tolterodine in urine incontinence in adults.
- Succinylcholine before endotracheal intubation.

Mention the pharmacodynamic principles underlying the contraindication of:

- Ergometrine (or ergotamine) during pregnancy.
- Alpha-blockers (or beta-blockers) alone in pheochromocytoma.
- Propranolol (beta-blockers) in bronchial asthma.
- Reserpine in parkinsonism.
- Bethanechol in urine retention due to senile enlarged prostate.
- Neostigmine to treat ms paralysis of organophosphate intoxicated patient.
- Atropine in closed angle glaucoma.
- Atropine in old patient with senile enlarged prostate.
- Atracurium in bronchial asthma.

Mention the rational of the following combinations:

- Alpha-blockers with beta-blockers in pheochromocytoma
- Atropine with neostigmine in myasthenia gravis.
- Caffeine with ergotamine in acute migraine.

Mention the main differences between:

- Dopamine and dobutamine.
- Ergotamine and ergometrine.
- Propranolol and atenolol.

Of each of the following questions, select ONE BEST answer:

1. Regarding adrenergic α1 receptors, all are true EXCEPT:

A. Molecular techniques revealed the presence of a number of subclasses.
B. Their stimulation can contract the pregnant human uterus.
C. Their stimulation can increase peripheral resistance
D. Their effect is more potent and shorter duration than β2 receptors.
E. Their activation leads to increase intracellular calcium

2. Regarding adrenergic β2 receptors, all are true EXCEPT:

A. Their stimulation can relax the non-pregnant human uterus.
B. Their activation on mast cells leads to stabilization of mast cell membrane.
C. Their activation leads to increase intracellular cAMP.
D. Their selective antagonists have no clinical uses.
E. Continuous and prolonged stimulation can lead to down-regulation

3. Stimulation of cardiac M2 cholinoceptors cause which of the following:

A. Decrease myocardial contractility
B. Decrease SA nodal activity and heart rate
C. Decrease conduction velocity through the Purkinje fibers
D. Decrease coronary blood flow
E. All of the above.

4. Physiological events mediated by stimulation of β1 adrenoceptors include all the following EXCEPT:

A. Increase insulin secretion
B. Increase systolic blood pressure
C. Shorten myocardial cell refractoriness
D. Increase outflow resistance in patients with obstructive cardiomyopathy
E. Increase renin release by juxtaglomerular cells of the kidney

5. Cholinergic stimulation causes:

A. Urine retention
B. Bronchodilatation
C. Sweating
D. Tachycardia
E. Reduced gut motility

6. Nicotinic acetylcholine receptors are found in all the following sites EXCEPT:

A. Sympathetic ganglia
B. Presynaptic nerve endings
C. Central nervous system
D. Skeletal muscles motor end plate
E. Vascular endothelium

7. Increased urinary levels of vanilyl mandelic acid (VMA) above 8 mg/24 hours is diagnostic marker of the following tumors:

A. Pheochromocytoma
B. Carcinoid tumor
C. Leukemia
D. Lymphoma
E. Astrocytoma

8. The actions of norepinephrine at adrenergic receptors are terminated by which of the following:

A. Metabolism by MAO in the liver
B. Reuptake into the nerve terminal
C. Conversion into 5-HIAA
D. Conversion to dopamine
E. None of the above

9. The following is true for true cholinesterase:

A. Is found in autonomic ganglia and myoneural junctions
B. Is found in plasma and liver
C. It needs 2 weeks to be regenerated
D. It can metabolize acetylcholine as well as other choline esters
E. Its presence is not necessary for life

10. Which of the following drugs acts indirectly by releasing norepinephrine?

A. Angiotensin
B. Dopamine

C. Phenylephrine
D. Amphetamine
E. Isoprenaline

11. Attention-deficit hyperactivity disorder in children can be treated by:
A. Ephedrine
B. Modafinil
C. Tizanidine
D. Methylphenidate
E. Midodrine

12. The following is correct about the action of sympathomimetics:
A. Adrenaline has almost exclusively β-adrenoceptor agonist actions
B. Noradrenaline has an approximately equal mix of α-and β-adrenoceptor agonist actions
C. Isoprenaline has predominantly α-adrenoceptor agonist actions
D. Phenylepherine has predominantly β-adrenoceptor agonist actions
E. Dopamine acts on specific D-receptors as well as other adrenoceptors.

13. Epinephrine, all are true EXCEPT:
A. It is a polar (ionized) compound.
B. Is synthesized from norepinephrine within the adrenal medulla
C. Cannot be administered orally.
D. It is available as eye drops for ophthalmic use.
E. The final product of metabolism is vanillylmandelic acid (VMA).

14. The following statements about the action of sympathomimetics (i.v.) are correct EXCEPT:
A. Adrenaline infusion causes rise in both systolic and diastolic blood pressure with tachycardia
B. Noradrenaline infusion causes rise in both systolic and diastolic blood pressure with bradycardia
C. Dopamine infusion causes decrease in renal blood flow and GFR.
D. Salbutamol causes fall of blood pressure with tachycardia
E. Phenylepherine causes rise of blood pressure with bradycardia

15. For the treatment of acute anaphylactic shock, adrenaline must be given by the following route:
A. Inhalation
B. Subcutaneous
C. Intravenous
D. Intramuscular
E. Intracardiac

16. Regarding reflex bradycardia induced by administration of vasopressor drugs:
A. It starts to work as a compensatory response after long time of vasopressor use
B. Reflex is mediated through stretch receptors in the left pulmonary artery
C. The receptors begin to respond at pressure ≥ 150 mmHg
D. In chronic hypertension the set point is shifted to a higher level
E. Beta blockers readjust the set point to a higher level

17. Dobutamine is best indicated for management of which the following shock:
A. Septic shock
B. Cardiogenic shock
C. Anaphylactic shock
D. Hypovolemic shock
E. Neurogenic shock

18. Ritodrine hydrochloride can be used in the management of:
A. Parkinson's disease
B. Bronchial asthma
C. Depression
D. Premature labor
E. Bradycardia

19. Selective α2 agonists that is used to relieve muscle spasm associated with a variety of neurological conditions is:
A. Clonidine
B. Tizanidine
C. Ritodrine

D. Midodrine
E. Alpha methyldopa

20. Nasal decongestants carry the risk of cerebral stroke in which of the following conditions:
A. Arterial hypertension
B. Allergic rhinitis
C. Epistaxis
D. Benign prostatic hypertrophy
E. Sinusitis

21. Oxymetazoline has which of the following actions:
A. Bronchodilation
B. Vasoconstriction
C. Hyperglycemia
D. Tachycardia
E. Inhibition of ejaculation

22. Chronic orthostatic hypotension due to impaired autonomic reflexes can be managed by:
A. Midodrine
B. Ritodrine
C. Amphetamine
D. Modafenil
E. Cocaine

23. 65 year old male requires extensive dental work. In your first session with him you inject lidocaine (2%) plus l: 100,000 epinephrine. Although there was initial anesthesia, you are surprised to discover that after 15 minutes the patient grimaces with pain when you work in the affected area. What is the best possible explanation?
A. The patient is a chronic complainer
B. The injection missed the appropriate nerves
C. The patient metabolizes lidocaine extra rapidly
D. The patient may suffer benign prostatic hypertrophy and is being treated with doxazosin
E. In this patient lidocaine is an ineffective local anesthetic

24. Which of the following drugs will decrease heart rate in a patient with a normal heart but will have no effect on heart rate in a cardiac transplant recipient?
A. Epinephrine
B. Salbutamol
C. Norepinephrine
D. Phenylephrine
E. Dopamine

25. False +ve test for antinuclear factor may be caused by:
A. Phenoxybenzamine
B. Prazosin
C. Reserpine
D. Yohimbine
E. Ergotamine

26. The following alpha blocker is best prescribed to decrease symptoms of urine retention due to senile enlarged prostate:
A. Prazosin
B. Tremazosin
C. Phenoxybenzamine
D. Terazosin
E. Tamsulosin

27. Alpha blockers can worsen which of the following urinary problems:
A. Urine retention due to senile enlarged prostate
B. Urine retention due to atonic bladder
C. Urine retention with over flow due to spinal cord injuries
D. Urine incontinence due to pelvic floor pathology in women
E. Dysuria and frequency associated with bladder inflammation

28. All the following conditions can be effectively treated by beta-blockers EXCEPT:
A. Angina pectoris
B. Essential hypertension
C. Raynaud's disease
D. Open angle glaucoma
E. Supraventricular tachycardia

29. The therapeutic action of beta-blockers in angina pectoris is believed to be primarily due to:

A. Reduced production of catecholamines
B. Dilatation of the coronary vessels
C. Decreased myocardial oxygen requirement
D. Increased peripheral resistance
E. Increased sensitivity to catecholamines

30. Beta-blockers are contraindicated in bronchial asthma because:

A. They produce bradycardia and fall in COP
B. They increase bronchial secretions
C. They decrease pulmonary blood flow
D. They increase airway resistance and narrowing
E. They inhibit the respiratory center and impair ventilation

31. Myocardial depression caused by overdose of beta blockers can be reversed by parenteral administration of:

A. Adrenaline
B. Dopamine
C. Isoprenaline
D. Glucagon
E. Insulin

32. Excessive bradycardia induced by beta-blockers is best treated by:

A. Dopamine
B. Epinephrine
C. Isoprenaline
D. Neostigmine
E. Atropine

33. Essential tremors can be best decreased by which of the following beta blockers?

A. Atenolol
B. Propranolol
C. Betaxolol
D. Nebivolol
E. Bisoprolol

34. The following beta-blocker is preferred to control tachycardia when peripheral vascular disease is also associated:

A. Propranolol
B. Dilevalol
C. Timolol
D. Pindolol
E. Sotalol

35. One of the following drugs is best chosen for the control of hypertension during pregnancy:

A. Captopril
B. Propranolol
C. Reserpine
D. Phenoxybenzamine
E. Alpha methyldopa

36. Positive Coomb's test and hemolytic anemia may follow the administration of:

A. Prazosin
B. Alpha methyldopa
C. Guanithidine
D. Reserpine
E. Clonidine

37. One of the following drugs should be avoided in the control of chronic hypertension associated with peptic ulcer:

A. Reserpine
B. Prazosin
C. Propranolol
D. Clonidine
E. Alpha methyldopa

38. The following statements about pilocarpine are correct EXCEPT:

A. It is a natural plant alkaloid
B. It acts selectively on muscarinic receptors
C. It can block the hypotensive effect of neostigmine
D. It is not metabolized by AChE enzyme
E. It has a clinically useful miotic action

39. The following statements about anti-ChE drugs are correct EXCEPT:

A. Physostigmine lowers IOP
B. Neostigmine may be used with atropine to treat myasthenia gravis
C. Pyridostigmine have fewer visceral side effects than neostigmine.
D. Rivastigmine can be used to treat paralytic ileus
E. Edrophonium has short duration of action

40. A central AChE inhibitor that is used to improve symptoms of Alzheimer's disease is:
A. Pyridostigmine
B. Edrophonium
C. Donepezil
D. Neostigmine
E. Echothiophate

41. A short acting AChE inhibitor used in the diagnosis of myasthenia gravis is:
A. Edrophonium
B. Neostigmine
C. Pyridostigmine
D. Rivastigmine
E. Donepezil

42. Which of the following drugs has the longest duration of AChE inhibition:
A. Echothiophate
B. Neostigmine
C. Physostigmine
D. Pyridostigmine
E. Donepezil

43. The cause of death in organophosphate toxicity is:
A. Bradycardia
B. Increased bronchial secretions
C. Paralysis of the respiratory muscles
D. Depression of the respiratory center
E. All of the above

44. All the following are known contraindications for the use of atropine EXCEPT:
A. Closed angle glaucoma
B. Senile prostatic enlargement
C. Paralytic ileus
D. Postpartum urine retention
E. Acute cystitis

45. Relatively selective muscarinic blocker that is used to treat urine incontinence in adults is:
A. Pyrenzepine
B. Benztropine
C. Ipratropium
D. Tolterodine
E. Oxybutinin

46. The metabolites of which of the following neuromuscular blockers can lead to seizures?
A. d-tubocurarine
B. Atracurium
C. Mivacurium
D. Vecuronium
E. Succinylcholine

47. When succinylcholine is used to provide muscle relaxation during delivery by cesarean section, the following is true:
A. It can cause fetal hypotonia and even fetal paralysis
B. It can relax the uterus and aggravate postpartum hemorrhage
C. It can cause acute hyperkalemia and arrest the heart of the fetus
D. It can cause maternal tachycardia
E. It can decrease the effect of general anesthetics

48. The following statements are true for neuromuscular blockers EXCEPT:
A. Succinylcholine can cause postoperative muscle pain.
B. Atracurium undergoes spontaneous plasma hydrolysis
C. Vecuronium breakdown products may cause seizures.
D. Neostigmine can reverse muscle block caused by competitive blockers
E. Synthetic derivatives are generally preferred than d-tubocurarine

49. A muscarinic blockers that is used as a standard treatment of motion sickness is:

A. Pirenzepine
B. Oxybutinine
C. Atropine
D. Scopolamine
E. Tolterodine

50. Zolmitriptan produce vasoconstriction of cerebral vessels and decrease pain mediators during acute migraine by acting on the following receptor subtypes:

A. 5HT 1B/1D
B. 5HT 1E/1F
C. 5HT 2A/2C
D. 5HT 3
E. 5HT 7

51. Bethanechol, a direct acting muscarinic agonist used for relieving post-operative urine retention in absence of organic obstruction, could not be given parenterally because:

A. It can cause annoying salivation
B. It can cause cardiac arrest
C. It can cause histamine release and severe anaphylaxis
D. It can cause urine leak out of control
E. It can cause undesirable nausea and vomiting

52. A muscarinic agonist given orally to increase salivary secretion and decrease symptoms of dry mouth associated with Sjögren syndrome is:

A. Cevimeline
B. Carbachol
C. Bethanechol
D. Pyridostigmine
E. Rivastigmine

53. Regarding the management of a patient with organophosphate toxicity, the following is true:

A. With most types of organophosphates, 90% of the enzyme undergoes aging within the first 3 hrs.
B. Pralidoxime is completely ineffective for enzyme regeneration after aging of the enzyme.
C. Pralidoxime is effective regardless AChE is phosphorylated (e.g. by organophosphates) or carbamylated (e.g. by neostigmine).
D. Atropine should not be stopped before systolic blood pressure rises above 110 mmHg and pulse rate above 100 bpm.
E. Diazepam should be given to reduce bronchospasm

54. Regarding the management of a patient with iridocyclitis, the following is true:

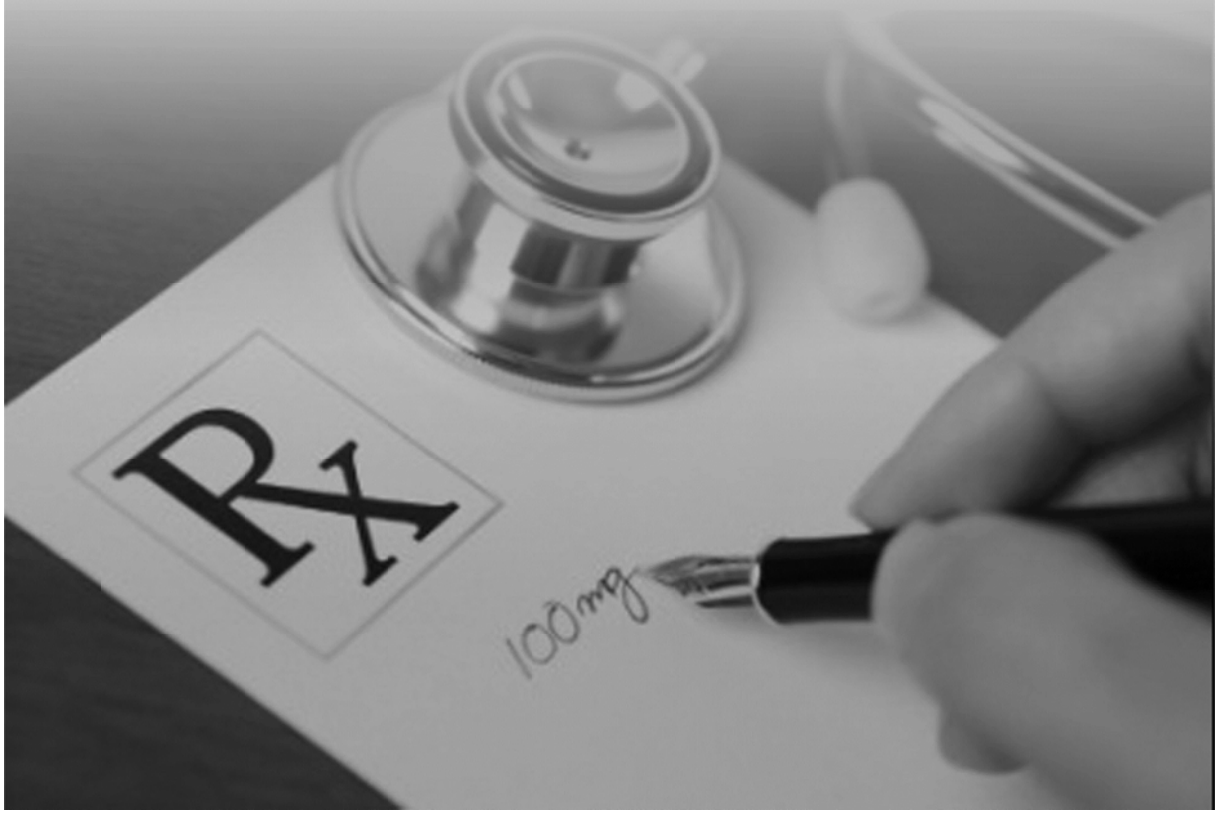
A. Mydriatics are used to help drainage of exudative fluids from the anterior chamber of the eye.
B. Short acting mydriatics such as phenylephrine are preferred to avoid prolonged blurring of vision
C. Atropine is preferred because it produces complete cycloplegia and mydriasis
D. If the patient was a child below 12 years old, atropine eye drops would be contraindicated.
E. Physostigmine eye drops should be used to help drainage of aqueous humor

Answers

1 D	12 E	23 D	34 B	45 D
2 B	13 A	24 D	35 E	46 B
3 B	14 C	25 B	36 B	47 C
4 A	15 D	26 E	37 A	48 C
5 C	16 D	27 D	38 C	49 D
6 E	17 B	28 C	39 D	50 A
7 A	18 D	29 C	40 C	51 B
8 B	19 B	30 D	41 A	52 A
9 A	20 A	31 D	42 A	53 B
10 D	21 B	32 E	43 E	54 C
11 D	22 A	33 B	44 E	

Chapter 3

Diuretic Agents And Volume Balance

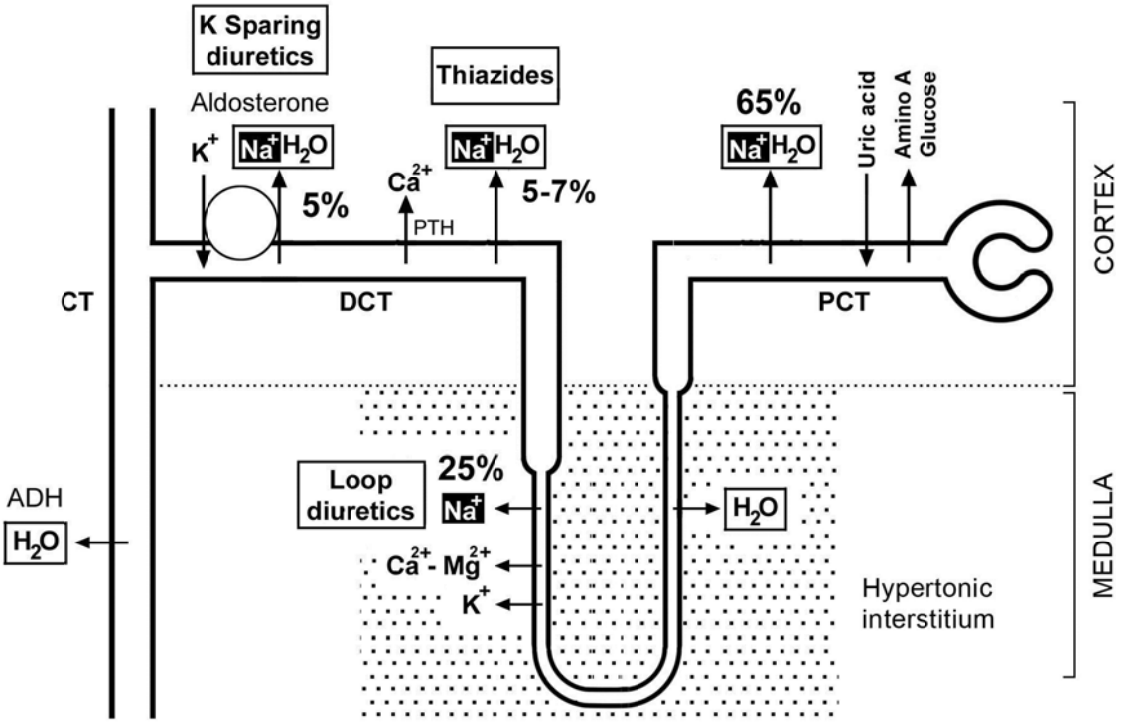


Chapter 3
Diuretic Agents and Volume Balance

Part 1: Basic information

TUBULAR FUNCTION AND URINE FORMATION

- The renal blood flow (RBF) is **1.1 L /min** (~ 22% of COP).
- The glomerular filtration rate (GFR) is **125 ml/min**.
- The capillary tuft filtrates ~ 180 L of fluid per day. 99% of the filtered fluid is reabsorbed again during passage in the renal tubules.
- Water reabsorption is usually **2ry to Na^+ reabsorption** (except in the collecting tubules; 'CT'). Any drug that ↓ Na^+ reabsorption (= ↑ Na^+ loss), also ↓ water reabsorption (= ↑ water loss or 'diuresis').



Tubular reabsorption and sites of action of 3 types of diuretics

- **Proximal convoluted tubules (PCT):**
  - **Reabsorption:** (75% of the glomerular filtrate).
    - Active reabsorption of Na^+ **(~65%).**
    - Passive (2ry to Na^+) reabsorption of equiosmotic amount of water.
    - Reabsorption of all filtered K^+, glucose, amino acids, and drugs.
  - **Secretion:** active secretion and reabsorption of organic acids and bases into tubular fluid.

- **Loop of Henle (LOH):**
  - **Descending limb:** passive reabsorption of water due to hypertonicity of the medullary interstitium.
  - **Ascending limb:** active reabsorption of Na^+ **(~25%)** (this causes hypertonicity of the medullary interstitium), Ca^{2+} and Mg^{2+}.

- **Distal convoluted tubules (DCT):**
  - **Proximal part:**
    - Active reabsorption of Na^+ **(5-7%).**
    - Passive (2ry to Na^+) reabsorption of equiosmotic amount of water.
    - Active reabsorption of **Ca^{2+}** (under the influence of **parathormone 'PTH'**).
  - **Distal part:**
    - Active reabsorption of Na^+ **(2–5%)** in exchange with K^+ (under the influence of **aldosterone**).
    - Passive (2ry to Na^+) reabsorption of equiosmotic amount of water.

- **Collecting tubules (CT):** Reabsorption of water under the influence of **ADH.**

EDEMA AND EDEMATOUS CONDITIONS

- Edema is defined as the accumulation of fluid in the interstitial space due to either:
  - Increased capillary hydrostatic pressure
  - Decreased plasma oncotic pressure.
  - Increased capillary permeability.
- Edema can be either **exudative** (having high protein content) or **transudative** (having low protein content).
- **Exudative edema** results from increased capillary permeability as part of the acute inflammatory response. It is usually localized to the site of inflammation and will not be considered in this chapter.

- **Transudative edema** is usually generalized and is associated with renal Na^+ retention. The three most common clinical causes are:
  - **Congestive heart failure (CHF):** the decreased COP causes renal ischemia which stimulates the renin-angiotensin-aldosterone system (RAAS) → Na^+ and water retention → edema.
  - **Liver cirrhosis:** the cirrhotic liver cannot synthesize sufficient albumin and other plasma proteins → ↓ plasma oncotic pressure. Hypoalbuminemia together with portal hypertension and 2ry stimulation of RAAS cause fluid retention (edema) and accumulation of fluid in the peritoneal cavity (ascites).
  - **Nephrotic syndrome:** glomerular dysfunction causes excessive loss of plasma proteins in urine → ↓ plasma oncotic pressure → edema.

Part 2: Diuretic classes and agents

Diuretics are drugs that increase urine volume and Na^+ excretion.
Natriuretic: a drug that increase Na^+ excretion by the kidney.

Classification of diuretics:

Renal diuretics	Extra-renal diuretics
They act directly on the kidney: ■ **Thiazide diuretics:** act on the proximal part of the DCT *e.g. hydrochlorothiazide.* ■ **Loop diuretics:** act on the ascending limb of loop of Henle *e.g. furosemide.* ■ **K^+ sparing diuretics:** act on the distal part of the DCT *e.g. spironolactone.* ■ **Osmotic diuretics:** substances that ↑ the osmotic pressure of tubular fluid → ↓ water reabsorption by renal tubules *e.g. mannitol.*	They act indirectly on the kidney: ■ **Water diuresis:** ↑ water intake → ↓ ADH release → diuresis. ■ **Digitalis in CHF:** ↑ the COP leading to ↑ RBF → diuresis. ■ **i.v. albumin in ascites or nephrotic edema:** to increase plasma osmotic pressure → mobilization of edema fluid toward the vascular compartment → ↑ RBF → diuresis.

N.B. **Carbonic anhydrase inhibitors** *e.g acetazolamide*: they are weak diuretics that ↓ $NaHCO_3$ reabsorption from the PCT and may cause **metabolic acidosis**. They also ↓ aqueous humor secretion and can be used in the treatment of glaucoma (see pharmacology of the eye).

Loop diuretics

(Furosemide, torsemide, bumetanide , and ethacrynic acid)

Pharmacokinetics

- They are absorbed from the GIT and secreted into the lumen of the PCT by an organic acid excretory system.
- The absorption of furosemide is erratic but bumetanide is complete.
- Diuresis occurs within **5** minutes after i.v. administration and within **30** minutes of oral administration.

Mechanism and pharmacological effects

- Loop diuretics **inhibit $Na^+/K^+/2Cl^-$ co-transport** system in the thick ascending limb of LOH leading to inhibition of the active reabsorption **Na^+**, **Cl^-**, and **K^+**. These ions are excreted with equiosmotic amount of **water**.
  - They also increase **excretion** of **Ca^{2+}**, **Mg^{2+}**, **halides** and **H^+**.
  - Na^+ and water loss at this segment is high, so they are **potent (or high ceiling)** diuretics (i.e., up to 25% of the filtered Na^+ load).
- They ↑ **renal PGE2 and PGI2** production leading to **VD** and ↑ RBF and GFR.
  - Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit PG synthesis and antagonize this effect of loop diuretics.
  - VD of **pulmonary** vascular bed also occurs due to ↑ PG formation.

Therapeutic uses

- **Edematous conditions:** e.g. CHF, nephrotic syndrome, etc.
  - Many patients require fluid and sodium restriction to have the best results.
  - Diuretics are **not used** to treat edema due to lymphatic obstruction (lymphedema) or inflammatory edema (localized edema with high protein content is difficult to be resolved by diuretics).
- **Acute pulmonary edema:** loop diuretic ↓ pulmonary congestion by:
  - They cause venodilatation → ↓ venous return.
  - They cause VD of pulmonary vascular bed even before diuresis occurs.
- **Acute renal failure:** to maintain adequate GFR and enhance K^+ excretion.
- Acute **hypercalcemia** and acute **hyperkalemia**: saline should be given to compensate for Na^+ and water loss.
- **Hypertensive emergencies:** i.v. furosemide is usually given in emergencies:
  - Loop diuretics ↓ plasma volume.
  - They cause peripheral VD due to ↑ PGs production in many vascular beds.
  - Hyponatremia ↓↓ sensitivity of the vascular smooth muscles to circulating catecholamines.

Adverse effects

- **Hypovolemia** and **hypotension.**
- **Electrolyte disturbances:** Hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia (all need to be properly replaced).
- **Hypokalemic metabolic alkalosis:** due to ↑ tubular secretion of K^+ and H^+.
- **Hyperuricemia** and precipitation of acute gout: This is caused by:
  - Increased uric acid reabsorption in the PCT as a result of hypovolemia (It may be prevented by using lower doses to avoid hypovolemia).
  - Competition with uric acid excretion at the organic acid excretory system in the PCT.
- **Ototoxicity:**
  - It is **reversible** hearing loss. It occurs with very **high** doses.
  - It may be due impairment of **ion transport** in the stria vascularis (inner ear).
  - Occurs more frequent with:
    - Patients with impaired renal function.
    - Ethacrynic acid.
    - Concomitant use of other ototoxic drugs e.g. aminoglycosides.
- **Allergic reactions:** all loop diuretics (except ethacrynic acid) are derivatives of sulfonamides; they cause occasional skin rash, eosinophilia, and less often, interstitial nephritis.

Thiazide diuretics

Classification

- **True thiazides** (they are derivatives of sulfonamides): hydrochlorothiazide, bendroflumethiazide.
- **Thiazide-like diuretics:** metalozone, indapamide, chlorthalidone.

Pharmacokinetics

- Thiazide diuretics are absorbed from the GIT. They are secreted into the lumen of the PCT by an organic acid excretory system.
- They produce diuresis within 1–2 hours.

Mechanism and pharmacological effects

- Thiazides **inhibit Na^+/Cl^- co-transport** system in the proximal part of **DCT** leading to inhibition of the active reabsorption **Na^+**, **Cl^-**. These ions are excreted with equiosmotic amount of **water**.
  - Excess **Na^+** reaching the DCT is reabsorbed in exchange with **K^+** (→ **K^+ loss).**

- They also increase **excretion** of **halides** and **H^+**.
- They ↓ **Ca^{2+} excretion** and enhance its reabsorption.
- Thiazides have **moderate efficacy** (i.e., maximum excretion of filtered Na^+ load is only 5-7%).
- Most thiazides are ineffective if the GFR is < 30-40 ml/min (so it is not useful, or even harmful, in presence of renal failure).

- The action of thiazides also depends on **renal PGs** like loop diuretics but to much less extent.

Therapeutic uses

- **Mild edematous states:** cardiac, hepatic, or renal (same as loop diuretics).
- **Essential hypertension** (mild to moderate)**:**
  - They have the same mechanisms like loop diuretics (mention them).
  - They are often combined with other antihypertensive drugs to enhance their blood pressure-lowering effects.
- **Hypercalcuria and renal Ca^{2+} stones:** to ↓ urinary **Ca^{2+}** excretion.
- **Nephrogenic diabetes inspipidus (DI):**
  - Thiazides can reduce urine volume in some cases of DI. This is called **"paradoxical antidiuretic action"** and it is not clearly understood. It may be due to improvement of ADH receptor sensitivity in the renal collecting tubules.

Adverse effects

- **Hypovolemia** and **hypotension.**
- **Electrolyte disturbances:** Hyponatremia and hypokalemia.
- **Hypokalemic metabolic alkalosis:** due to ↑ tubular secretion of K^+ and H^+.
- **Hyperuricemia** the same as with loop diuretics.
- **Hyperglycemia:** due to both ↓ pancreatic release of insulin and ↓ tissue utilization of glucose.
- **Hyperlipidemia:** due to ↑ cholesterol and LDL (by 5-15%).
- **Allergic reactions:** thiazides are derivatives of sulfonamides; they cause occasional skin rash, dermatitis, and less often, thrombocytopenia.

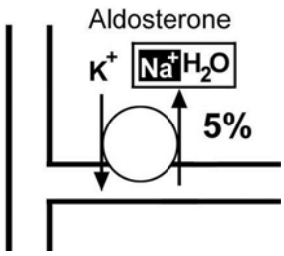
Potassium-sparing diuretics
(Spironolactone – triameterine – amiloride)

- Spironolactone is a **steroid** congener of aldosterone.
- Triamterene and amiloride are synthetic drugs **but not steroids.**

Pharmacokinetics

- All are absorbed from the GIT.
- Spironolactone and triamterene are metabolized by the liver
- Amiloride is excreted unchanged in the urine.
- They have **slow onset** (days).

Mechanism and pharmacological effects



- **Site of action:** the distal part of the DCT where Na^+ is reabsorbed (**2–5%**) in exchange with K^+ under the influence of **aldosterone**.
- **Spironolactone** is a competitive antagonist of aldosterone at its receptor site at the distal part of DCT leading to ↑ Na^+ excretion (with excretion of equiosmotic amount of water) and K^+ retention.
- **Triamterene and amiloride** are **direct inhibitors** of Na^+ channels in the distal part of DCT leading to ↑ Na^+ excretion (with excretion of equiosmotic amount of water) and K^+ retention.

- **The net effect is:**

– Mild Na^+ and water loss (i.e., maximum excretion of filtered Na^+ is only 2-5%)
– Hyperkalemia: due to ↓ K^+ excretion (K^+ will be retained in blood).
– Metabolic acidosis: due to ↓ H^+ ion excretion (H^+ will be retained in blood).

Therapeutic uses

- **All cases of edema due to hyperaldosteronism:**
  - Primary hyperaldosteronism: e.g. Conn's disease.
  - Secondary hyperaldosteronism: e.g. in liver cirrhosis or nephrotic syndrome.
- **Used in combination with loop diuretics or thiazides in order to:**
  - To minimize the risk of electrolyte imbalance:
    Loop diuretics cause hy**po**kalemia while K^+ sparing diuretics cause hy**per**kalemia. Their combination can minimize electrolyte disturbance.
  - To minimize the risk of acid-base imbalance:
    Loop diuretics cause metabolic alkalosis while K^+ sparing diuretics cause metabolic acidosis. Their combination can minimize acid-base imbalance.
  - To make synergism in cases of refractory (resistant) edema.
- **Treatment of female pattern hair loss**:

  Spironolactone is a weak competitive inhibitor of **androgens** at their receptors and ↓ synthesis of testosterone (antianderogenic effect). Some dermatologists use this feature to stop androgen-related frontal hair loss in women.

Adverse effects

- **Hyperkalemia** due to ↓ K^+ excretion.
- **Hyperkalemic metabolic acidosis:** due to ↓ K^+ and ↓ H^+ excretion.
- Spironolactone has **antiandrogenic effects** (gynecomastia and impotence in males).

N.B.

Eplerenone is a similar congener of spironolactone. It has little antiandrogenic effects but more hyperkalemic effects.

Contraindications

- **All cases of hyperkalemia:** especially in the following conditions:
  - Patients with chronic renal failure.
  - With drugs that cause hyperkalemia e.g. ACEIs.
- **Spironolactone should not be given with carbenoxolone** because carbenoxolone has aldosterone-like action and can antagonize the effect of spironolactone.

	Spironolactone	Triamterene - amiloride
Structure	Synthetic steroid	Synthetic non-steroids
Metabolism	Extensive metabolism in the liver	Amiloride is excreted unchanged in urine
Mechanism of action	Competitive antagonism with aldosterone at its receptor site in the DCT	Direct inhibition of Na^+ channels at the distal part of DCT
Antianderogenic efcts	Gynecomastia & impotence	Not present

Osmotic diuretics: Mannitol, Glycerol

They are chemically inert substances given by **i.v. infusion** in **emergency** conditions

Mechanism of action

- First, they ↑ osmotic pressure of plasma leading to withdrawal of transcellular fluid (e.g. aqueous humor, excessive CSF, etc).
- Second, they are freely filtered by the glomerulus and ↑ osmotic pressure of the tubular fluid leading to ↓ water reabsorption by renal tubules.

Therapeutic uses

Acute congestive glaucoma and acute rise in intracranial pressure: they are given by i.v. infusion for rapid ↑ drainage of of aqueous humor or CSF respectively by increasing the osmotic pressure of the plasma before diuresis begins.

Adverse effects: dehydration with hypernatremia is the main adverse effect.

Comparison between the 3 main classes of diuretics

	Loop diuretics	Thiazides	K+ sparing diuretics
Site of action	thick ascending limb of LOH	proximal part of DCT	distal part of DCT
Mechanism	Inhibit $Na^+/K^+/2Cl^-$ co-transport system	inhibit Na^+/Cl^- co-transport system	Spironolactone is a competitive antagonist of aldosterone Triamterene and amiloride are direct inhibitors of Na^+ channels in the distal part of DCT
Efficacy	High	Moderate	Mild
Onset	Rapid (minutes)	Less rapid (hours)	Slow (days)
Serum K+	Hypokalemia	Hypokalemia	Hyperkalemia
Blood pH	Metabolic alkalosis	Metabolic alkalosis	Metabolic acidosis
Ca2+ excretion	↑	↓	--
Use in renal failure	Can be used	Not effective or harmful	Contraindicated
Use in hypertension	Hypertensive emergencies	Mild essential hypertension	In combination with other diuretics
Blood glucose	Little or no effect	Rise	Little or no effect
Plasma lipids	Little or no effect	Rise	Little or no effect
Ototoxicity	Common	Less common	Rare

Part 3: Advantages and disadvantages of diuretics in some edematous conditions

CONGESTIVE HEART FAILURE (CHF)

Patients with CHF have ↓COP due to weak cardiac muscle, fluid retention, and lung congestion. Many patients have also high blood pressure.

Advantages of diuretics:

- Correction of fluid retention.
- Lowering of blood pressure.
- Decrease preload (venodilatation and ↓ venous return) and afterload (due to arterial VD) leads to improvement of cardiac contraction.
- Decrease lung congestion causes improvement of tissue oxygenation.
- Recent evidence showed that **spironolactone** reduces morbidity and mortality rates in patients with advanced heart failure.

Disadvantages of diuretics:

- Excessive hypovolemia can ↓ COP.
- Diuretic-induced acid-base and electrolyte imbalance may impair cardiac function.
- Diuretic-induced **hypokalemia** can predispose to digitalis toxicity and cardiac arrhythmia.

Recommendation: Combination between a K^+ sparing diuretic and loop diuretic is the best choice.

CHRONIC KIDNEY DISEASES

The majority of patients with chronic renal diseases (e.g. chronic renal failure, diabetic nephropathy, etc.) have fluid retention**,** hypertension, hyperkalemia**,** and acidosis.

Advantages of diuretics:

- Correction of fluid retention.
- Reduction of hyperkalemia.
- Reduction of hypertension.

Recommendation: Loop diuretics are best choice.

Disadvantages of diuretics:

- Thiazides are **ineffective** when GFR is <30 ml/min, moreover it may be harmful.
- K^+ sparing diuretics are **contraindicated** because they can exacerbate hyperkalemia and acidosis.
- Carbonic anhydrase inhibitors (acetazolamide) are **contraindicated** because they can exacerbate acidosis.

LIVER CIRRHOSIS

Patients with chronic liver disease have fluid retention, ascites, hyperammonemia and 2ry hyperaldosteronism.

Advantages of diuretics:

- Correction of fluid retention.
- Spironolactone antagonizes aldosterone.

Disadvantages of diuretics:

- Aggressive use of diuretics can precipitate hepatorenal syndrome.
- Aggressive use of diuretics can precipitate hyperammonemia and hepatic **encephalopathy**. **How?**

- Normally, the urine pH is acidic (~5.6). In acidic urine, most of the absorbable **ammonia** (NH3) is converted into the non-absorbable **ammonium** ions (NH4+) and so it is removed out by the kidney (this is known as ammonia trapping).

- Diuretics cause hypokalemia and metabolic alkalosis. This leads to:
  - Systemic alkalosis causes the pH of the urine to become less acidic. This decreases conversion of the urinary absorbable NH3 into the non-absorbable NH4. The excreted NH3 is thus reabsorbed again from urine to blood → **hyperammonemia**.
  - Systemic alkalosis increases the **entry** of NH3 into the brain cells.

Hepatorenal syndrome

- Functional oliguric RF occurring in a patient with advanced liver disease in absence of other causes of RF. The renal histology is normal.

- The pathogenesis of HRS is not fully understood. Disturbance in renal hemodynamics due to imbalance between renal VC and VD mechanisms may be responsible.

- Prognosis is poor.

Recommendation:
Aldosterone antagonists such as spironolactone are suitable choice in hepatic patients to help prevent the formation of ascites. A loop diuretic may need to be added in refractory cases.

LOWER LIMB EDEMA DURING PREGNANCY

- Lower limb edema during late pregnancy is common condition and is usually benign (physiologic). It occurs due to hormonal imbalance, and compression of pelvic veins by the enlarged uterus.
- Unilateral leg edema, redness, warmth, and tenderness require evaluation for deep venous thrombosis (DVT).
- Physiologic edema can be reduced by elevating the lower extremities and wear elastic stockings.

– Diuretics are better avoided during pregnancy because they effectively **reduce maternal plasma volume** and consequently may reduce amniotic fluid and/or placental blood flow.

Part 4: Volume depletion and fluid replacement

- Volume depletion can be caused by loss of blood or other body fluids e.g. vomiting, diarrhea, etc.
- In cases of mild volume depletion, resuscitation can be adequately achieved with oral fluid alone. Sodium chloride tablets and electrolyte-containing solutions are often used.
- In cases of severe dehydration, i.v. fluid therapy is preferred and may be life-saving.
- Water alone is not an appropriate fluid for volume resuscitation since it enters the cells by osmotic effect. Only one third of each administered liter remains in the extracellular space, and only one twelfth of each administered liter remains in the intravascular space.
- When electrolyte disturbances are present, the fluid used for resuscitation should be chosen to correct both volume depletion and electrolyte disturbances.

Crystalloid solutions

■ **Sodium chloride solutions:**

– **Normal saline (0.9% NaCl):** It is the most commonly used solution. It contains 154 mEq sodium per litre, a concentration similar to the sodium concentration of plasma. Due to the relatively high chloride content, normal saline carries a risk of inducing hyperchloraemic metabolic **acidosis** when given in large amounts.

– **Hypotonic saline (0.45% NaCl):** contains 77 mEq sodium per liter, and can be used when there is dehydration with hypernatraemia. In these patients, 5% dextrose in water can be given simultaneously with normal saline.

– **Hypertonic saline (3% NaCl):** contains 513 mEq sodium per liter, and can be used for management of acute hyponatremia.

■ **Lactated Ringer's solution:**

– It is an isotonic solution containing sodium, potassium, chloride, calcium and lactate. The lactate is metabolized by the liver into bicarbonate, which can help correct metabolic **acidosis**. In lactic acidosis and **liver disease** this conversion is impaired, so lactate-containing fluids should be avoided.
– It is **not suitable for maintenance** therapy because the Na^+ and K^+ contents are too low to compensate for daily electrolyte requirement.

■ **Glucose (Dextrose) solutions:**

- Various concentrations are available e.g. 5%, 10% and 25%. The 5% dextrose in water (also known as D5W) is isotonic and is the most commonly used.
- Hypertonic glucose solutions (above 5%) should be infused very slowly and cautiously to avoid **hyperosmolar syndrome** and life-threatening **dehydration**.

Colloid solutions

- Colloids are classified as either natural (**albumin** and **fresh frozen plasma**) or artificial (**starch** and **dextran**).
- They preserve a high colloid **osmotic pressure** in the blood and theoretically designed to increase the intravascular volume with much less effect on tissue water. However, colloid solutions are a less-preferred choice for the management of volume depletion because they are very expensive and have not shown a mortality benefit over isotonic saline.

Oral rehydration therapy (ORT)

- Oral electrolyte solutions are used in **children**, particularly with gastroenteritis. This product contains sodium, potassium, chloride, citrate, and dextrose, and is designed to replace the electrolytes and water that are lost with vomiting or diarrhea.
- Glucose is typically added to these oral replacement solutions to promote uptake of sodium via the intestinal sodium/glucose co-transporter mechanism.

Part 5: Disorders of serum sodium and potassium

Hyponatremia and SIADH

Normal serum Na^+ is **135-145** mEq/L

- Hyponatremia is defined as serum Na^+ <135 mEq/L. It can be caused by any medical illnesses, such as CHF, liver failure, renal failure, pneumonia, or SIADH.
- Severe hyponatremia (Na^+ <120 mEq/L) leads to fall of plasma osmolality, with movement of water from plasma to brain and other cells causing neurological manifestations (altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, coma or seizures).
- ADH (or vasopressin) is released from posterior pituitary in response to high plasma osmolality. It binds to three receptors: **V1a** in the vasculature (VC), **V1b** in the brain, and **V2** in renal collecting ducts (↑ water absorption).
- When the ADH system is working properly, 'the urine should reflect the blood', i.e. concentrated urine occurs when plasma osmolality is high, and vice versa.

- Many factors (including drugs and other non-pharmacological conditions) can stimulate release of ADH irrespective of plasma osmolality, leading to **hyponatremia**, a condition known as **"syndrome of inappropriate ADH secretion"** or **SIADH.**

Drugs that cause SIADH:
Carbamazepine
Chloropropamide
Cytotoxic drugs
Opiates

Management of SIADH

- **Fluid restriction** (1L/d) is the main line.
- **Demeclocycline** and **lithium** may be "rarely" used; they impair the response of the collecting ducts to ADH (by a non-receptor mechanism).
- **Vasopressin receptor antagonists: "Vaptans":**
  - Antagonism of the V2 receptors results in aquaresis, a unique electrolyte-free water excretion by the kidneys.
  - **Conivaptan** is a mixed V1a and V2 antagonist, and **tolvaptan**, a selective V2 antagonist.
  - **Tolvaptan** is approved for treating hyponatremia associated with heart failure, cirrhosis, and SIADH.
  - Recent studies showed that vaptans may be more effective in treating hypervolemia in heart failure than diuretics.

Hypernatremia

- Hypernatremia is defined as a plasma Na^+ >145 mEq/L, and represents a state of hyperosmolality
- Hypernatremia may be caused by a primary **Na+ gain** or a **water loss**, the latter being much more common. **Renal water loss** results from either **osmotic diuresis** or **diabetes insipidus (DI)**.
- Hypernatremia results in contraction of brain cells as water shifts to attenuate the rising ECF osmolality. Thus, the most severe symptoms of hypernatremia are neurological manifestations.

N.B.

Aggressive correction of hyper- or hyponatremia is potentially dangerous. The rapid shift of water into- or- from brain cells increases the risk of seizures or permanent neurologic damage.

Management of symptomatic hypernatremia

- The mainstay of management is the administration of **water**, preferably by mouth or nasogastric tube. Alternatively, 5% dextrose in water (D5W) can be given intravenously.
- Specific therapy of the underlying cause.

Hypokalemia

Normal serum K^+ is 3.5-5 mEq/L

- Potassium is the major intracellular cation. 98% of K^+ in the body is found in the intracellular compartment, leaving 2% in extracellular fluid spaces.
- Renal K^+ excretion occurs from the DCT and is mediated by aldosterone and Na^+ delivery to the distal nephron.
- Hypokalemia is defined as serum K^+ <3.5 mEq/L. It can result from diminished K^+ intake, transcellular shift of K^+, or increased K^+ loss.
- The most common **manifestations** are muscle weakness, cramps, flattened T wave and prolonged QT interval in the ECG.
- Because K^+ is usually exchanged with H^+ at the DCT, hypokalemia is often linked to metabolic alkalosis. Anyone of these two conditions can lead to the other.

Drugs cause transcellular shift of K^+ (from plasma to tissue):
Insulin and beta-2 agonists: they ↑ transmembrane Na^+/K^+-ATPase activity.

Drugs cause renal loss of K^+:
Mineralocorticoids, glucocorticoids, diuretics, amphotericin-B.

Drugs cause GIT loss of K^+: laxatives

Management

- Patients with a K^+ level of **2.5-3.5** mEq/L may need only oral K^+ replacement
- If the K^+ level **< 2.5** mEq/L, intravenous K^+ should be given. The rate of infusion should not exceed 20 mEq/hr, Rapid IV infusion may cause serious arrhythmia or even cardiac arrest.
- Hypomagnesemia is frequently associated with hypokalemia. Concomitant magnesium deficiency aggravates hypokalemia and renders it difficult to treatment by K^+ alone.

Hyperkalemia

- Hyperkalemia is defined as serum K^+ >5 mEq/L. It can result from transcellular shift of K^+, or decreased renal excretion of K^+ (as in chronic renal failure).
- The most common **manifestations** are muscle paralysis, palpitations, high peaked T wave and short QT interval in the ECG.
- Because K^+ is usually exchanged with H^+ at the DCT, hyperkalemia is often linked to metabolic acidosis.

Drugs cause transcellular shift of K^+ (from tissue to plasma):
Insulin deficiency and β-blockers: they ↓ transmembrane Na^+/K^+-ATPase activity.

Drugs that ↓ renal excretion of K^+:
K+ sparing diuretics, ACEIs, NSAIDs, cyclosporins.

Management

- **Mild hyperkalemia:** could be corrected by diuretics and oral cation exchange resins (Polystyrene sulfonate) to promote the exchange of Na^+ for K^+ in the GIT.
- **Severe hyperkalemia with ECG changes:**
  - Intravenous calcium gluconate to reduce cardiac toxicity (↓ membrane excitability). The usual dose is 10 mL of a 10% solution infused over 2 to 3 minutes.
  - Intravenous insulin with glucose: 20 U regular insulin mixed with 500 ml D5W.
  - Correct metabolic acidosis with i.v. NaHCO3 solution.
  - Hemodialysis is reserved for patients with renal failure or with life-threatening hyperkalemia resistant to other treatment.

Part 6: Pharmacological manipulation of the urine pH

Normal urine pH is 5.2-6.5. It is possible, by the use of pharmacological agents, to produce urinary pH values ranging from ~ 5 to 8.5.

Alkalinization of the urine

- **Indications:**
  - To enhance excretion of acidic drugs and organic compounds e.g. aspirin, sulfonamides, and uric acid.
  - To enhance dissolution of uric acid and cystine stones.
  - To relieve dysuria (burning micturition) in some cases of bladder infection.
- **Alkalinizing agents:**
  - **Oral:** sodium and potassium citrate salts: citrate is metabolized into bicarbonate which is excreted in urine.
  - **Intravenous** bicarbonate solution: contains 5% NaHCO3.

Acidification of the urine

- **Indications:**
  - It is rarely used clinically except in a specialized test to discriminate between different kinds of renal tubular acidosis.
  - It can be very dangerous in cases of renal or hepatic impairment.
- **Acidifying agents:**
  - **Oral:** ascorbic acid > 2 g/d.
  - **Intravenous** ammonium chloride (NH4Cl) solution.

Notes

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Review Questions

Mention the pharmacodynamic principles underlying the use of:

- Furosemide in arterial hypertension.
- Furosemide in acute pulmonary edema.
- Thiazides in diabetes insipidus.

Mention the pharmacodynamic principles underlying the contraindication of:

- Furosemide in acute hyperuricemia.
- Thiazides in uncontrolled diabetes mellitus.
- Spironolactone in chronic renal failure.
- Amiloride with ACEIs.
- Ethacrynic acid with aminoglycosides.
- Furosemide with NSAIDs.

Mention the advantages and disadvantages of diuretics in the following conditions:

- Congestive heart failure.
- Chronic kidney disease.
- Chronic liver disease.

Mention the rational of the following combination:

- Furosemide with spironolactone.

Mention 3 differences between:

- Furosemide and spironolactone.

Of each of the following questions, select THE ONE BEST answer:

1. The ascending part of the loop of Henle is the principal site of action of the following diuretics:
A. Hydrochlorothiazide
B. Triamterine
C. Amiloride
D. Bumetanide
E. Spironolactone

2. Hyperkalemia is a contraindication of the following diuretics:
A. Furosemide
B. Bumetanide
C. Ethacrynic acid
D. Chlorothiazide
E. Spironolactone

3. Loop diuretics are clinically useful in the treatment of all the following edematous states EXCEPT:
A. Edema caused by congestive heart failure
B. Edema caused by chronic liver failure
C. Lymphedema
D. Nephrotic syndrome
E. Ankle edema due to chronic hydralazine treatment

4. Intravenous albumin is the ideal choice for treatment of the following conditions:
A. Ascites due to chronic liver disease
B. Edema due to chronic kidney disease
C. Edema due to congestive heart failure
D. Lymphedema
E. Inflammatory edema

5. Vigorous diuretics are contraindicated in resistant ascites due advanced liver disease because:
A. It can lower blood pressure to a critical level
B. It can precipitate hepatorenal syndrome
C. It can lead to severe dehydration
D. It can decrease ascetic fluid suddenly and drastically
E. It aggravate hypoalbuminemia

6. Which of the following diuretics can enhance the parathormone-mediated calcium reabsorption from the distal renal tubules:
A. Hydrochlorothiazide
B. Triamterine
C. Amiloride
D. Bumetanide
E. Spironolactone

7. Idiopathic calcium urolithiasis (hypercalciuria) can be treated by:
A. Hydrochlorothiazide
B. Ethacrynic acid
C. Furosemide
D. Triamterine
E. Bumetanide

8. Spironolactone is characterized by:
A. It interferes with aldosterone synthesis
B. It competitively inhibit aldosterone action in the distal part of the distal renal tubules
C. It inhibits sodium reabsorption in the proximal renal tubules
D. It is more potent diuretic than hydrochlorothiazide
E. It has rapid onset and short duration

9. Hydrochlorothiazide is clinically useful in the treatment of all the following conditions EXCEPT:
A. Edema caused by congestive heart failure
B. Edema caused by chronic liver failure
C. Edema caused by chronic renal failure
D. Hypertension with or without edema
E. Recurrent calcium urolithiasis

10. Adverse reactions associated with thiazide therapy include all the following EXCEPT:
A. Hyperglycemia
B. Hyperuricemia
C. Metabolic acidosis
D. Fluid and electrolyte imbalance
E. Hypotension

11. All the following diuretics can aggravate digitalis toxicity EXCEPT:
A. Hydrochlorothiazide

B. Furosemide
C. Bumetanide
D. Amiloride
E. Ethacrynic acid

12. Adverse effects of loop diuretics include all the following EXCEPT:
A. Magnesium deficiency
B. Sodium deficiency
C. Hypoglycemia
D. Hypovolemia
E. Hyperuricemia

13. Hypokalemia can be caused by all the following drugs EXCEPT:
A. Captopril
B. Salbutamol
C. Thiazides
D. Corticosteroids
E. Insulin

14. The following statements are true concerning the precautions during the use of diuretics in different metabolic disorders EXCEPT:
A. Furosemide may enhance digitalis toxicity in congestive heart failure
B. Furosemide may aggravate hyperammonemia in chronic liver failure
C. Chlorothiazides may aggravate renal impairment in chronic renal failure
D. Thiazides may aggravate hyperglycemia in diabetes mellitus
E. Thiazides may increase formation of urinary uric acid crystals in chronic gout

15. All the following drugs can produce salt and water retention after their prolonged use EXCEPT:
A. Nifedipine
B. Minoxidil
C. Amiloride
D. Prazosin
E. Hydralazine

16. Adverse reactions associated with furosemide therapy include all the following EXCEPT:
A. Hearing loss
B. Hyperuricemia
C. Metabolic alkalosis
D. Fluid and electrolyte imbalance
E. Hypercalcemia

17. Acute pulmonary edema is best treated by i.v. administration of:
A. Hydrochlorthiazide
B. Furosemide
C. Mannitol
D. Amiloride
E. Metalozone

18. Which of the following diuretics has the highest potential to cause ototoxicity:
A. Chlorothiazide
B. Furosemide
C. Ethacrynic acid
D. Acetazolamide
E. Spironolactone

19. All the following are uses of loop diuretics EXCEPT:
A. Acute pulmonary edema
B. Severe hypertension
C. Acute hypercalcemia
D. Acute oliguria
E. Calcium urolithiasis

20. In an addisonian patient, all of the following agents would have diuretic action EXCEPT:
A. Mannitol
B. Chlorothiazide.
C. Bumetanide
D. Furosemide.
E. Spironolactone

21. Gynecomastia may occur with the use of the following diuretics:
A. Chlorothiazide
B. Furosemide
C. Amiloride
D. Acetazolamide
E. Spironolactone

22. The most dangerous complication of injudicious use of diuretics in patients with advanced liver diseases is:

A. Aggravation of hypotension and fatigue
B. Electrolyte imbalance
C. Acid-base imbalance
D. Precipitation of hepatorenal syndrome
E. Marked dehydration

23. Acute congestive glaucoma is best treated by i.v. administration of:
A. Bumetanide
B. Furosemide
C. Mannitol
D. Amiloride
E. Metalozone

24. The following statements concerning hypokalemia are true EXCEPT:
A. It is a side effect predicted with all diuretics
B. It is commonly seen in patients with hyperaldosteronism
C. It can be manifested by ECG changes
D. It could be prevented by the use of K+ sparing diuretics
E. It is a risk factor for digitalis toxicity

25. The best intravenous agent given to patients with advanced liver disease to correct ascites and edema is:
A. Human albumin
B. Mannitol
C. Furosemide
D. Chlorothiazide
E. Spironolactone

26. A 63-year-old man presents to the emergency department with worsening heart failure. Physical exam reveals pitting edema in his ankles. Past medical history is significant for an allergic reaction following exposure to trimethoprim–sulfamethoxazole. Which drug should the physician prescribe to him?
A. Acetazolamide
B. Ethacrynic acid
C. Hydrochlorothiazide
D. Mannitol
E. furosemide

27. A 64-year-old woman with congestive heart failure. She complains of swelling in her legs and ankles. The doctor decides to increase her level of diuretics. What complication should the doctor be most aware of for this patient?
A. Diuretic-induced metabolic acidosis
B. Hepatic encephalopathy
C. Hypercalcemia
D. Hyperkalemia
E. Hypokalemia

28. One of your clinic patients is being treated with spironolactone. Which of the following statements best describes a property of this drug?
A. Contraindicated in heart failure, especially if severe
B. Inhibits Na+ reabsorption in the proximal renal tubule of the nephron
C. Interferes with aldosterone synthesis
D. Is a rational choice for a patient with an adrenal cortical tumor
E. Is more efficacious than hydrochlorothiazide in all patients who receive the drug

29. A patient taking an oral diuretic for about 6 months presents with elevated fasting and postprandial blood glucose levels. You suspect the glycemic problems are diuretic-induced. Which of the following was the most likely cause?
A. Acetazolamide
B. Amiloride
C. Chlorothiazide
D. Spironolactone
E. Triamterene

30. Chlorthalidone and torsemide are members of different diuretic classes, in terms of mechanisms of action, but they share the ability to cause hypokalemia. Which of the following statements best describes the general mechanism by which these drugs cause their effects that lead to net renal loss of potassium?
A. Act as aldosterone receptor agonists, thereby favoring K+ loss

B. Block proximal tubular ATP-dependent secretory pumps for K+
C. Increase delivery of Na+ to principal cells in the distal nephron, where tubular Na+ is transported into the cells via a sodium channel in exchange for K+, which gets eliminated in the urine
D. Inhibit a proximal tubular Na,K-ATPase such that K+ is actively pumped into the urine
E. Lower distal tubular urine osmolality, thereby favoring passive diffusion of K+ into the urine

31. Which of the following is a clinical indication for use of Mannitol?
A. Chronic simple glaucoma
B. Cerebral edema
C. Pulmonary edema
D. Acute heart failure
E. chronic renal failure

32. All the diuretics act from the luminal side of the renal tubule EXCEPT:
A. Torsemide
B. Hydrochlorothiazide
C. Spironolactone
D. Chlorthalidone
E. Furosemide

33. A 55-year-old male with kidney stones has been placed on a diuretic to decrease calcium excretion. However, after a few weeks, he develops an attack of gout. Which diuretic was he taking?
A. Furosemide.
B. Hydrochlorothiazide.
C. Spironolactone.
D. Triamterene
E. Acetazolamide

34. Your 60 year old male hypertensive patient who had a myocardial infarction a year ago is now showing signs of CHF. You therefore add spironolactone to his drug regimen. What side effect should you warn him about?
A. Gynecomastia
B. Hypokalemia
C. Lupus
D. Ototoxicity
E. Hyperuricemia

Answers

1 D	11 D	21 E	31 B
2 E	12 C	22 D	32 C
3 C	13 A	23 C	33 B
4 A	14 E	24 A	34 A
5 B	15 C	25 A	
6 A	16 E	26 B	
7 A	17 B	27 E	
8 B	18 C	28 D	
9 C	19 E	29 C	
10 C	20 E	30 C	